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THE EFFECT OF REM SLEEP DEPRIVATION ON STIMULUS-BOUND FEEDING THRESHOLDS IN RATS

by

RONNIE HALPERIN

A doctoral dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirement for the degree of Doctor of Philosophy, The City University of New York.

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Abstract

THE EFFECT OF REM SLEEP DEPRIVATION ON STIMULUS-BOUND FEEDING THRESHOLDS IN RATS

by

Ronnie Halperin

Adviser: Professor Steven J. Ellman

Rapid eye movement (REM) sleep deprivation and amphetamine administration have many similar behavioral effects. Both treatments increase spontaneous motor activity, lower thresholds for intracranial self-stimulation (ICSS) and increase various measures of aggression. Furthermore, both have been reported to facilitate the learning of simple tasks while interfering with learning of more complex tasks. In humans, clinical improvement of endogenous depression has been reported in response to both REM deprivation and amphetamine.

This experiment was designed to explore the relationship of a waking motivated behavior (feeding) to REM sleep. Stimulus-bound eating (SBE) behavior, elicited through electrical stimulation to the lateral hypothalamus (LH), is believed to reflect motivated eating behavior.

Amphetamine exerts a paradoxical effect upon ICSS and SBE behavior elicited from the same electrode in that ICSS thresholds are lowered, while SBE thresholds are elevated following amphetamine administration.

If the similarities noted between amphetamine and REM deprivation occur across other motivated behaviors, then, contrary to the hypothesis that REM deprivation should decrease thresholds for all motivated behaviors, one would predict that SBE thresholds would be elevated, rather than lowered following REM deprivation. This experiment comprises a systematic attempt to determine the effects of REM deprivation upon SBE thresholds at two different times during the circadian feeding cycle, and utilizing two different threshold assessment procedures.

Each of sixteen rats was implanted with a bipolar electrode, aimed at the LH, and apparatus for recording electroencephalograph (EEG) and electromyograph (EMG). Animals displaying SBE behavior were tested daily at varying stimulation intensities on one of two threshold assessment procedures (R-50 or multiple ascending) until stable eating thresholds were determined. Half the animals in each threshold procedure were tested at three hours after the onset of the dark period, and half were tested at ten and one-half hours after the onset of the light period in their day-night cycle.

Thresholds were assessed daily throughout the duration of the experimental paradigm, which consisted of two days of adaptation (A), five days of baseline (BL), five days of either REM deprivation or stress control and five days of recovery (R). The inverted flower-pot technique was utilized to achieve REM deprivation or stress control. Approximately two weeks after the termination of the R condition, the entire paradigm was run again, this time utilizing the experimental condition not previously run. Animals were monitored for EEG and EMG during all conditions.

After termination of the sleep manipulations, nine rats were

tested for SBE thresholds in response to amphetamine treatment. Polygraphic data indicate that rats tested in the light were significantly more REM deprived during REM deprivation than control conditions. Animals tested in the dark did not respond differentially to the two platform conditions.

All rats exhibited elevated threshold in response to both treatment conditions when compared to BL levels. Animals tested in the light exhibited significantly greater increases over BL levels in response to REM deprivation than control conditions. There was no significant difference in the increase in threshold over BL levels during REM deprivation as compared to control conditions for animals tested in the dark.

The data refute the hypothesis that REM deprivation lowers thresholds for all motivated behaviors. On the contrary, it suggests that the mechanisms mediating the behavioral effects of REM sleep deprivation may be the same as those mediating the response to amphetamine.

Acknowledgement

I would like to thank Dr. Steven J. Ellman and Dr. Solomon S. Steiner, not only for their guidance in the execution of this study, but for their concern for my education and my happiness throughout my years in graduate school. They have taught me how to pose important questions and set about answering them, and therefore they will always be responsible for the great sense of fulfillment I derive from conducting research.

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Many students at the City College of New York have spent long and hard hours assisting in collection of the data for this experiment. I thank them all.

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Sleep

Historically, it had been believed that sleep served a restorative function. Furthermore, sleep was viewed as a uniform state that varied along a continuum in depth (see Berger, 1969). This long-standing view was challenged in 1953 when Aserinsky and Kleitman discovered, in human subjects, a sleep stage that was qualitatively different from sleep as it had been understood until that time. This sleep state was characterized by bursts of rapid conjugate eye movements and central neural activation in the presence of behavioral quiescence. The simultaneous occurrence of desynchronous cortical electroencephalograph (EEG), rapid conjugate eye movements and relative muscle atonia (as compared to both waking and other sleep states) define REM sleep. (Particular behavioral criteria for defining REM sleep will be specified below for humans and rats.) In addition, rate of heart beat and respiration are elevated and become more variable (Aserinsky & Kleitman, 1953; Snyder, Hobson, Morrison, & Goldfrank, 1964). Metabolic rate (Brebbia & Altschuler, 1965) and brain temperature (Kawamura & Sawyer, 1965) are increased, and in males, penile erection occurs during REM sleep (Fisher, Gross, & Zuch, 1965; Karacan, Goodenough, Shapiro, & Starker, 1966).

Initially, REM sleep was associated with dreaming. Early studies examining the occurrence of dream reports during awakenings from various sleep stages reported that dreaming occurred as much as 88% of the time after awakenings from REM sleep and as little as 0% of the time subsequent to awakenings from non-REM (NREM) sleep (Dement, 1955). Later studies (Goodenough, Lewis, Shapiro, Jaret, & Slesser, 1965) report as much as a 34% frequency of dream reports after awakenings from NREM sleep and

only a 69% frequency of dreaming in response to awakenings from REM sleep. The discrepancy between these studies has been attributed to the fact that the criteria defining dreaming were set by the subjects in the earlier study and by the experimenter (as any mental content) in the later study (Berger, 1969). Molinari and Foulkes (1969) found that dream reports resulting from REM sleep awakenings were bizarre and contained much sensory experience, whereas reports from NREM awakenings were of a more cognitive nature. More recently, REM versus NREM mentation reports have been found to be distinguishable by blind raters based on amount of visual imagery, hallucinatory content and bizarreness (Arkin, Antrobus, Ellman, & Farber, 1978).

REM sleep has been found to occur in all mammals tested (see Snyder, 1969 for review), and in a more fragmented form in avian predators (Klein, 1963). The existence of REM sleep in its fully developed form in the opossum, an animal that is believed to resemble early mammalian species more than any presently surviving mammal (see Snyder, 1969), suggests that REM sleep may in some way be a uniquely mammalian phenomenon.

The extent to which sleep is consolidated over the day varies among species. The daily human sleep cycle is biphasic; the sleep cycle of many mammals, however, is polyphasic. Sleep in the rat is characterized by many oscillations between slow-wave sleep (SWS), REM sleep and waking throughout the day. During SWS, a slow, high amplitude EEG reflects synchronous firing of cortical units. Behavioral quiescence may or may not be accompanied by a decreased muscle tonus. During REM sleep and waking, desynchronous cortical neuronal firing is reflected by low amplitude, mixed frequency EEG and rapid, conjugate eye movements. In addition, theta

waves originating from firing of hippocampal units are present in the EEG. However, during waking, rats display high muscle tonus whereas during REM sleep, muscle atonia prevails throughout the state (Van Twyer, 1966). Weiss and Roldan (1964) report an average of 108 REM periods per day with an average duration of 127 seconds per episode in the rat.

In humans, sleep is conventionally divided into five stages (Rechtschaffen & Kales, 1968). Stage I (also known as descending Stage I) occurs immediately upon the absence of waking and is defined in terms of the absence of alpha (8-12 Hz) waves and the presence of slow, rolling eye movements accompanied by behavioral quiescence. Stage II is characterized by a slower EEG and the appearance of fast, monophasic sharp waves known as K-complexes, and brief bursts of rapid firing, known as spindles, in the EEG. Stages III and IV are characterized by the appearance of delta waves (1-2 Hz) in the EEG, high thresholds for awakening and low muscle tonus, compared to waking. During Stage IV, delta waves occupy a larger percentage of the EEG than during Stage III. REM sleep is characterized by a mixed frequency, low amplitude wave occurring in the EEG. Concurrently, low muscle tone, rapid eye movements and in males, penile erection, occur. During the night, sleep onset (Stage I) is followed by Stages II, III, and IV, after which the cycle ascends to Stage III, II, and then REM sleep. During subsequent cycles, Stage I is omitted. The cycle occurs about five times per night and has a mean duration of approximately 90 minutes (Berger, 1969). During the first half of night, sleep cycles are longer and more time is spent in Stages III and IV, while during the latter part of the night, there is little

delta sleep and a predominance of REM and Stage II (Webb, 1969). REM sleep occupies as much as 48.8% of total sleep time in newborn infants (Roffwarg, Muzio,& Dement, 1966) and decreases to about 32% by age two years (Kohler, Coddington, & Agnew, 1968). In adults, REM sleep comprises approximately 23% of total sleep time (Webb, 1969).

The neurophysiological and neurochemical mechanisms mediating sleep have been investigated extensively. Based on studies conducted on the cat, Jouvet (1967) has hypothesized that serotonergic cells of the pontine raphe nuclei mediate SWS and exert a priming influence on REM sleep. He has hypothesized that REM sleep is mediated through firing of ascending noradrenergic cells in the posterior two-thirds of the pontine locus coeruleus in the cat (Jouvet, 1967), and the rat (Jouvet, 1974), and that the muscle atonia associated with REM sleep is mediated through active inhibition by descending posterior noradrenergic locus coeruleus units. In support of Jouvet's theory are reports that: 1) parachlorophenylalanine (a drug known to inhibit synthesis of serotonin at the hydroxylase stage) and raphe lesions both result in insomnia (Jouvet, 1967, 1969a); 2) locus coeruleus lesions and 6-hydroxydopamine (a drug known to destroy noradrenergic nerve terminals through uptake) injections both result in selective abolition of REM sleep (Jouvet, 1969b); and 3) single unit studies report selective increases in firing rates of noradrenergic locus coeruleus cells during REM sleep (Chu & Bloom, 1973). Contradictory evidence includes reports that: 1) locus coeruleus lesions do not result in the abolition of REM sleep, but merely in a decrement and redistribution of ponto-geniculate occipital (PGO) spiking typically associated with the occurrence of REM sleep in the cat (Jones, Harper, &

Halaris, 1977); 2) 6-hydroxydopamine lesions do not abolish muscle atonia during REM sleep (see Jones et al., 1977); 3) alpha-methyl-paratyrosine (a drug known to inhibit synthesis of norepinephrine at the hydroxylase stage) increases REM sleep (Jouvet, 1973); and 4) single unit studies report decrements in firing rates of raphe units during slow wave sleep as compared to waking (McGinty, Harper, & Fairbanks, 1973) and selective decrements in firing rates of locus coeruleus units during REM sleep (Siegal & McGinty, 1976; Hobson, McCarley, & Wyzinski, 1975).

An alternative hypothesis has been proposed, suggesting that REM sleep is mediated by cholinergic cells in the area of the vestibular nuclei (Pompeiano, 1970) and particularly by the gigantocellular units in the tegmental fields (FTG) of the pons, which are proposed to be REM sleep generator cells (Hobson & McCarley, 1971). Evidence for this hypothesis based on studies conducted in the cat, include the facts that 1) firing of vestibular units are temporarily linked to phasic events (such as PGO spikes) (Pompeiano, 1970); 2) the FTG neurons selectively increase firing rates during REM sleep (Hobson & McCarley, 1971); and 3) firing of locus coeruleus neurons which probably exert an inhibitory influence postsynaptically and which have been shown to decrease firing rates during REM sleep, occurs in a reciprocally timed sequence to firing of FTG neurons (Hobson et al., 1975). Recently, McCarley, Nelson and Hobson (1978) have reported on a group of dorsal brainstem cells in apposition to the brachium conjunctivum. They suggest that these units function as output generators of PGO spikes. These cells fire in bursts of two to six spikes and show a high degree of PGO wave coherence. Bursts

occur 12 msec. before the onset of PGO waves. These investigations suggest that the events leading to PGO spike generation begin with firing of FTG units (possibly as a result of disinhibition by locus coeruleus or raphe neurons) resulting in activation (possibly through occulomotor or vestibular nuclei) of the PGO burst neurons which integrate information from other pontine systems and act as PGO output generator neurons.

Siegal and McGinty (1977) and Vertes (1977) have criticized the assertion that FTG units serve as REM sleep generator neurons. While Hobson and McCarley (1971) have demonstrated that large rate increases in the firing of FTG units are linked to the occurrence of REM sleep, Siegal and McGinty suggest that this selective increase in firing rate is an artifact of Hobson and McCarley's use of head restraints for cats during recording periods. They report that increased firing of FTG units is closely linked to specific head and neck movements. Specifically, they find that rate of movement correlates with unit firing rate. Siegal and McGinty assert that FTG unit firing during REM sleep reflects firing of motor units that also fire during waking, and propose that the lack of selective REM-linked rate increases in firing argues against the notion that they are REM-generator neurons.

A. REM Sleep and Behavior

1. Methodological Considerations. The behavioral significance of REM sleep was investigated primarily through studies that examined changes in behavior resulting from REM sleep deprivation. Since most animals have polyphasic sleep cycles, REM deprivation had to be administered either by consolidating the sleep cycle (through total sleep deprivation for part of the day) and then employing selective REM depri-

vation techniques, or through REM-deprivation procedures that were in effect throughout the day. This was accomplished either through the use of the inverted flower-pot technique or through administration of a drug that selectively inhibits REM sleep. The inverted flower-pot technique entails placing the animals on a small platform surrounded by water. The platform used is large enough to permit the animal to exhibit NREM sleep but small enough so that when the muscle atonia associated with REM sleep occurs, the animal's loss of postural tonus causes it to make contact with the water and to be automatically awakened. Drugs that have commonly been used as REM-deprivation agents are imipramine, sodium pentobarbital, and amphetamine.

Several confounds are introduced through the use of any REM deprivation procedure, however, a more basic issue is the question of whether, in fact, the animal is being REM-deprived, and whether it is being selectively REM-deprived (as opposed to sleep-deprived). The degree of REM deprivation and NREM deprivation can be measured directly if EEG and EMG are monitored throughout the baseline and deprivation conditions, or it can be inferred from recording during baseline and recovery by measuring the degree of compensation for each sleep state.

Utilization of drugs for REM deprivation requires that saline controls be employed. Amphetamine reduces NREM sleep latency (Rechtschaffen & Maron, 1964), while sodium pentobarbital enhances NREM sleep and decreases sleep latency (Baekeland, 1967). It is known that these drugs affect a wide variety of behaviors, and therefore the use of any particular drug may be inappropriate, depending on the behavior to be examined in response to REM deprivation.

The platform technique is stressful (Stern, 1969) and there-

fore requires control procedures. Even if a perfect stress control procedure were employed, the outcome could be the result of an interaction between REM deprivation and stress. Stress control has been attempted through two methods: 1) cold water stress in which animals are placed in cold water for a brief (3 minutes to 2 hours) time period once daily (Stern, 1971); and 2) large platform control, in which animals are maintained on platforms similar to those used in REM deprivation (Duncan, Henry, Karadzic, Mitchell, Pivik, Cohen, & Dement, 1968; Mendelsohn, Guthrie, Frederick, & Wyatt, 1974; Mouret, Pujol, & Kiyuno, 1969; Morden, Conner, Mitchell, & Dement, 1968a); these platforms are large enough so that the loss of postural tonus need not result in contact with the surrounding water. The problem with the cold water stress is the degree to which it differs from the stress of the platform treatment, since it is an acute rather than a chronic stress, and that it increases activity levels while the platform technique decreases activity levels. The problem with the large platform control is that some REM deprivation occurs and frequently as much as 50-80% REM deprivation has been reported (Stern, 1971). In that case, it is important that significantly different amounts of REM deprivation occur in REM deprivation and large platform conditions, and behavioral changes must be assessed in terms of the difference in the magnitude of change over baseline level.

In assessing behavioral changes in response to REM deprivation, changes in sensitivity to either environmental stimuli, or to experimental manipulations resulting from the REM deprivation treatment must be considered. Such change may result in a change in the potency of various experimental conditions. For example, food deprivation or shock treatment may be more or less potent under conditions of REM deprivation.

Potency of stimulus conditions can exert a confounding influence on performance.

A small group of studies has attempted to understand the behavioral significance of REM sleep by examining the effect of waking behavior on the sleep cycle. The implication of this approach is that, in addition to maintaining some kind of physical milieu (cortical tone, chemical homestasis) to facilitate a process mediating behavior (i.e. learning, memory, motivation), the REM sleep mechanism exerts modulation by being interchangeable with waking behavior. In these studies, it is essential that certain methodological considerations be made. In order to assert that REM sleep has been selectively enhanced in response to behavioral or environmental events, it is necessary to show that the increase cannot be accounted for by an increase in SWS. It is known that SWS levels predict REM sleep levels in the absence of other manipulations (Ferguson & Dement, 1967). In addition, in order to assert that an augmentation occurred immediately subsequent to the experimental manipulation, it is necessary to record for at least 24 hours to assess whether the effect is truly an enhancement of sleep effect or whether it is merely a shift in the circadian cycle resulting from the experimental manipulation.

In those cases where a selective suppression of REM sleep occurs, it is important to record for an extended time period to determine whether the REM time was compensated for.

2. Experimental Findings. REM deprivation has been shown to result in an increased number of attempts to enter REM sleep, decreased REM sleep latency, and increased time spent in REM sleep in terms of absolute time, or as a percentage of total sleep time in most mammals (for

review, see Snyder, 1969).

The hypothesis that REM sleep is a time during which information is consolidated or stored has been investigated by Greenberg and Pearlman (1974), Fishbein (1970, 1971, 1974), and Hartmann and Stern (1972). Greenberg and Pearlman (1974) have hypothesized that REM sleep serves as a period during which unusual information is stored in memory. They divide learning situations into those necessary for the animal's survival and those in which assimilation of new information is necessary. The former are REM-independent, while the latter need to be consolidated during REM sleep. According to Greenberg and Pearlman, it is crucial that the REM sleep occur during the two hours immediately subsequent to the learning experience for the information to be available for storage. In a series of experiments using rats, they tested for retention of what they believed to be REM-independent and REM-dependent tasks (Greenberg, Pearlman, Fingar, Kantrowitz, & Kawliche, 1970; Greenberg, Pillard, & Pearlman, 1972; Pearlman, 1973; Pearlman & Greenberg, 1973; Pearlman & Becker, 1974, 1975). In all experiments, animals were trained, REM-deprived during the two hours immediately following training (or treated with control procedures), and then tested for retention. The learning tasks for REM-independent behaviors included allowing the animals to explore a simple cage with a niche (Pearlman, 1971) containing food, and extinction of an operant task (Pearlman, 1973). REM deprivation did not interfere with acquisition of these tasks. Latent extinction (Pearlman, 1973), cooperative learning (Pearlman & Becker, 1975), and latent learning (Pearlman & Becker, 1974) were inhibited by REM deprivation administered during the two hours immediately subsequent to training. If REM

deprivation procedures were administered after a two-hour delay, retention was not interfered with.

Pearlman and Greenberg used a variety of REM deprivation techniques to demonstrate their effects. In one study (Pearlman & Greenberg, 1973) aimed at making a point of converging evidence, they used three methods of REM deprivation: 1) sodium pentobarbital; 2) imipramine; and 3) inverted flower-pot technique. They did not, however, use appropriate controls for any of these manipulations (saline, dose-dependent effects, large platform controls). In addition, polygraphic recordings were not used to validate the REM-deprivation manipulation.

Fishbein has attempted to show that REM sleep is necessary for the consolidation of a memory trace from short- to long-term storage. In a series of four studies employing mice, he tested retention after training of a passive avoidance task in conjunction with REM deprivation. He found that three days of REM deprivation administered subsequent to a one-trial passive avoidance training session disrupted retention if subjects were tested one hour, but not one day, after REM deprivation (Fishbein, 1971). In a second study, he utilized a similar paradigm, but in conjunction with administration of ECS at various intervals after termination of REM deprivation (Fishbein, McGaugh, & Swarz, 1971). He found that ECS administered immediately after passive avoidance training disrupted retention when mice were tested one day later, however, if ECS was delivered six hours after termination of REM deprivation, retention was not affected. Fishbein suggests that REM deprivation keeps the memory trace in a labile form, thus making it available for a brief period and disruptable by ECS.

He conducted two studies utilizing a different paradigm. REM deprivation was administered prior to passive avoidance training and retention was tested up to one hour or one to seven days subsequent to training (Fishbein, 1970). Retention tested more than one hour subsequent to training was interefered with following REM deprivation. Fishbein suggests that REM deprivation leads to a state in which consolidation to long-term memory is not possible. In a similar study (Linden, Bern, & Fishbein, 1975), he combines this paradigm with ECS administration delivered at various time after passive avoidance training. ECS delivered three hours after passive avoidance training (or longer) does not result in impaired retention. Again, in a REM-deprived animal, this memory trace cannot be fixed in long-term storage and remains in a labile form.

Thus, in one series of experiments in which mice were trained and then REM deprived, Fishbein found that performance assessed shortly after REM deprivation was disrupted. In a second series, in which REM deprivation preceded training, performance was intact for as long as six hours after training. As noted by Ellman, Spielman, Luck, Steiner, and Halperin (1978), from the standpoint of a memory-consolidation hypothesis these studies yield contradictory results. If REM deprivation produces a (chemical) milieu that interferes with consolidation into long-term storage, then animals should be in identical states after REM deprivation and passive avoidance training regardless of which occurred first. In the first series of experiments, the animals seemed to have access to the labile memory trace, while in the latter, they did not. Ellman and coworkers (1978) suggest that this can be explained by the fact that the animals always performed best when tested in the same condition as that

in which they were trained (state-dependent effects). No stress control groups were used in these studies.

Stern (1971) and Hartmann and Stern (1972) have shown that REM deprivation interferes with acquisition and retention of both active and passive avoidance tasks. They compare animals that were REM deprived through use of the inverted flower-pot technique to animals maintained in their home cages. While they found no differences between REM-deprived animals and large platform controls, they attribute this to the fact that large platform treatment results in 50% REM deprivation. Nonetheless, if significant differences in REM deprivation are administered, differences in performance would be predicted if REM deprivation, and not stress, were the crucial variable.

Several studies have found that REM deprivation is ineffective in disrupting acquisition or retention of various tasks. Joy and Prinz (1969) found that retention of a pole-climbing task was disrupted only when animals were tested in environmental conditions different than those used during training (state-dependent effects). Albert, Cicala, and Siegal (1970) found that REM deprivation did not affect retention of a shuttle-box avoidance task, but that activity levels were increased in response to REM deprivation. Holdstock and Verschoor (1973) found that retention of a position response in a T-maze task was not affected by REM deprivation. In all tasks in which REM deprivation was not effective in disrupting retention or acquisition, simple tasks were used and therefore, collectively, these studies lend support to Pearlman and Greenberg's hypothesis. Their findings, however, have not necessarily been demonstrated to reflect disruption of a consolidation mechanism. It may be the case that a procedure such as REM deprivation creates a perturbance that dis-

rupts some other mechanism determining performance. Thus, Pearlman and Greenberg's hypothesis distinguishing between unprepared and prepared learning remains a viable, although not conclusive, position.

A series of studies in rats and mice have reported an augmentation of REM sleep following conditioning of footshock avoidance. Lucero(1970), Hennevin, Leconte, and Bloch (1971), Leconte and Hennevin (1973), Leconte, Hennevin, and Bloch (1973), and Smith, Kitahama, and Valatx (1972) all found increased REM sleep in the three hours immediately following conditioning compared to yoked controls. The REM sleep augmentation appeared without concomitant increases in SWS or sleep latency. Hennevin and co-authors (1971) report that the increase is accounted for by increased duration of REM periods while Smith and coworkers (1972) and Leconte, Hennevin, and Bloch (1973) report that the number of REM periods, rather than the duration of each episode, accounts for the augmentation effect. When training sessions are distributed, the increase in REM sleep peaks at about the third hour of training (Hennevin et al., 1971; Smith et al., 1972; and Leconte et al., 1973) and REM levels return to baseline when the cumulative learning curve assymptotes (Leconte et al., 1973). In these studies, polygraphic data were recorded for the three to five-hour period subsequent to training each day. Thus, one cannot rule out the possibility that these effects are due to shifts in the circadian rhythm of the sleep cycle.

Fishbein, Kastaniotos, and Chattman (1974), using a conditioned avoidance task in mice, reported a long-term augmentation in REM sleep that occurred between six and 24 hours after conditioning trials. Unlike the investigators previously discussed, this study did not report REM increases in the few hours subsequent to training. This discrepancy

cannot be accounted for by species differences since Smith and co-workers (1972) and Fishbein both employed mice as subjects. Furthermore, the task that Fishbein utilized has been used by other investigators. There is some question as to whether result of Fishbein's experiment was selective REM augmentation. The animals in the experimental group exhibited SWS levels that were higher than those exhibited by control mice. Fishbein notes that this difference does not reach significance. Nonetheless, experimental subjects had a 24% increase in SWS, while control subjects had only a 10% increase. A more appropriate control would comprise a group of subjects with more comparable SWS levels. Furthermore, when each group is compared to its own pre-training sleep level, SWS occupies 89% of total sleep time in both experimental and yoked control groups pre- and post-training.

REM deprivation has been shown to lower thresholds for electroconvulsive shock (ECS) in the rat (Cohen & Dement, 1965; Owen & Bliss, 1970), the cat (Cohen, Duncan, & Dement, 1967; Cohen, Thomas, & Dement, 1970), and in the mouse (Handwerker & Fishbein, 1975; Hartman, Marcus, & Leinoff, 1968; Cohen & Dement, 1968). In addition, rats treated with ECS exhibit decreased levels of REM sleep, and REM-deprived rats treated with ECS exhibit decreased REM rebound (Kaelbling, Koski, & Hartwig, 1968). Although polygraphic data is lacking in these studies, and in some appropriate controls were not used, the consistency of the results among the studies compels one to conclude the validity of the results. Ellman et al. (1978 have suggested that increased neural excibility can account for the combined effect of ECS and REM deprivation on the disruption of performance that is observed in Fishbein's studies and offer this explanation as an alternative to the memory-consolidation hypothesis.

It has been hypothesized that REM sleep is a period during which excess "drive" energy is dissipated and that REM sleep is a behavioral manifestation of drive energy (Dement, 1969). According to this hypothesis, REM deprivation should result in increased waking drive behavior. Dement hypothesized that REM sleep serves as a "safety valve" for excess drive energy held in reserve for use during environmentally challenging situations. He refers to findings that REM-deprived cats displayed an enhancement of drive behaviors including hyperactivity, hyperphagia, hyperdipsia, and hypersexuality (Dement, 1965, 1969). These findings were not published and have not been replicated. In light of the popularity of this theory, relatively few studies have investigated the relationship between REM sleep and waking motivated behaviors.

Studies examining the relationship between REM sleep and feeding include a reference (but not a report) by Dement (1965) to the finding that cats exhibited increased lever-pressing for food if REM-deprived only when they were treated under conditions of food deprivation. In addition, Siegal (1975) found that REM percent of total sleep time on a given day was negatively correlated with food intake on the following day. Food intake, however, for a given day did not predict subsequent REM levels. Interestingly, in Siegal's study, one cat displayed a significant positive correlation. These findings are important; however, in context with the dearth of investigations in this area, it is difficult to hypothesize the mechanism mediating the relationship between REM sleep and feeding. For example, feeding alterations may have been a result of increased activity levels, increased hunger, or attentional alterations.

Four studies report a relationship between REM sleep and aggressive behavior. Morden and co-workers (1968a) found that thresh-

olds for foot-shock-induced fighting were lowered in rats in response to deprivation (as compared to large-platform controls). During recovery conditions, however, thresholds did not return to baseline levels. Sloan (1972) found that aggression, as measured by the Klein-Hall rat aggression scale, increased in response to REM deprivation. Putkonen and Putkonen (1971) found that elicitation of the hypothalamic rage response through electrical stimulation of the medial forebrain bundle resulted in decrements in REM sleep. In REM-deprived cats, the same treatment results in decrements in REM rebound. The REM suppression was evidenced by decreased REM percent of total sleep time, and increased latency to REM sleep. (Increased REM latency was associated with enhanced SWS rather than changes in waking time.) These investigators recorded for 15 hours and 24 hours subsequent to elicitation of the rage response in normal and REM-deprived rats respectively. Therefore, it is difficult to assess whether REM sleep was delayed or compensated for by the stimulation treatment. Ferguson and Dement (1969) found that amphetamine treatment combined with REM deprivation resulted in a significant enhancement of aggressive behavior as measured by time spent in stereotypic fighting behavior. Experimental animals were compared to controls treated with amphetamine and large-platform conditions, and amphetamine and dry environments. The authors suggest that amphetamine and REM deprivation may exert parallel effects, and that their combined effects may be either additive or synergistic.

Ferguson and Dement (1969) also report increased mounting and inappropriate sexual behavior in response to REM deprivation in combination with amphetamine treatment. In female rats, vaginal smears were analyzed and no changes were observed. Morden, Mullins, Levine, Cohen,

and Dement (1968b) reported in an abstract that REM deprivation in rats resulted in an increase in copulatory behavior; however, this study has not been published elsewhere.

Steiner and Ellman (1972), in a study that utilized large-platform controls and polygraphic monitoring throughout all conditions, found that REM deprivation lowered thresholds and increased lever-pressing rates for intracranial self-stimulation (ICSS) delivered to the lateral hypothalamus in rats. In addition, REM-deprived rats administered two hours of ICSS daily displayed a significantly lower REM rebound than controls. These findings have been replicated by Cohen, Edelman, and Bowen (1972). In a later experiment from the same laboratory (Spielman, Ellman, Halperin, Davis, Schwartz, Marks, Halperin, & Steiner, 1974) it was found that hypothalamic ICSS administered for two hours daily, increased latency to REM sleep, but neither altered daily levels of REM nor resulted in REM rebound. In a follow-up experiment, they found that if stimulation was delivered for two hours every six hours (i.e., four equally-spaced two-hour sessions daily), REM latency was increased and overall daily REM levels were lowered by 19%. This treatment resulted in a 50% REM rebound. In addition, these authors have found a significant correlation ($r = +.4$) between REM percent of total sleep time and rate of ICSS during the following stimulation session. There were no significant correlations between waking or SWS and ICSS rate. The same authors investigated the effects of ICSS elicited from bilateral locus coeruleus brain sites on the normal sleep cycle in rats. They found a 16% reduction in REM sleep and a 30% REM rebound. Ellman and co-workers (1978) have hypothesized that a reward system that can be mapped by ICSS sites is part of the neural system that is activated during REM sleep.

This system discharges in conjunction with certain waking behaviors (in association with rewarding experiences) as well.

3. Theories. Diverse theories as to the behavioral significance of REM sleep served as the bases for the experiments described above. Many of these theories have been directed towards explaining a few compelling features characterizing the REM sleep state. Physiologocically, the paradoxical nature of REM sleep (central neural activation and peripheral deactivation) is unique. In addition, the relationship of this physiological state to the psychological dream state (Dement, 1965) seemed to hold answers to questions raised by psychoanalytic theory regarding the relationships of the dream to waking behavior (Freud, 1969). Other compelling phenomena include the fact that organisms exhibit a "stored need" for REM sleep as reflected by REM rebound (Dement, 1960; Berger, 1969), the phylogenetic association of REM sleep to mammals (Snyder, 1969), and the fact that neonates exhibit elevated REM sleep levels (Roffwarg et al., 1966). Following are summaries of theories that attempted to explain the behavioral function of REM sleep.

Drive Theory. Based on the facts that: 1) organisms exhibit a "stored need" for REM sleep; and 2) dreaming appears to have a strong association with the REM sleep state, Dement (1969) has hypothesized that REM sleep is a manifestation of excess drive energy. He reasons that the activation of pre-programmed behaviors organized at the level of the brainstem may be determined by an energy system that must be able to respond to environmental challenge. In order to function as a drive system, it might have to energize behavior at a level beyond the capacity afforded by its basal metabolic rate, and it would therefore need storage capacity. In addition, organisms should be able to emit these behaviors strategically

and therefore must be able to suppress drive appropriately. A system that accumulates energy without leakage would need a safety valve process. Since REM sleep is a time during which extensive neural activity can occur without behavioral consequence, it could serve as an appropriate time to dissipate excess drive energy stores. This is the function he ascribes to REM sleep.

It follows from this notion that when animals are deprived of REM sleep, stored drive energy levels should be elevated and that, conversely, if the animal were to utilize a great deal of this energy during waking, the system could be temporarily depleted. If it is assumed that under conditions of elevated (or unsafe) storage levels the drive system would dissipate during waking, then one would predict a lowering of thresholds for drive behaviors in response to REM deprivation. In addition, after a behavioral episode in which this system were depleted, REM sleep onset might be delayed. As described above, studies reporting a relationship between aggressive behavior and REM sleep in rats (Ferguson & Dement, 1969; Morden et al., 1968a; Putkonen & Putkonen, 1971) support this hypothesis. That REM deprivation of endogenous depressives results in alleviation of symptoms (Vogel, Traub, & Ben-Horin, 1968) lends additional support to this notion. A non-specific drive hypothesis, however, is not supported by the negative results in studies (except Siegal, 1975) that investigated changes in feeding and sexual behavior in response to REM deprivation. In addition, the findings of Pearlman (1973), Pearlman & Becker (1974, 1975), Greenberg and co-authors (1970, 1972, 1974) which fail to find an enhancement of behavior for simple tasks, provide contradictory evidence for the drive hypothesis.

Sentinel Theory. Based on the facts that: 1) REW sleep is

mediated by pontine brain mechanisms that existed early in phylogenetic history; 2) although fragmented aspects of REM sleep have been reported in lizards (Tauber, Roffwarg, & Weitzman, 1966) and birds (Klein, 1963), REM sleep in its fully developed state appears only in mammals; 3) REM sleep occurs in all mammals (Snyder, 1969); and 4) evidence suggests that at the beginning of mammalian phylogeny REM sleep was already fully developed (Snyder, 1969), Snyder (1969) has hypothesized that the occurrence of REM sleep served as an adaptation crucial to the survival of early mammals. Snyder has suggested that increased amounts of sleep during the time when small mammals existed concurrently with large, ferocious reptiles would have aided survival by keeping the organism unobtrusive and by lowering his nutritional requirements. In addition, periods of arousal in which the animal could respond to an impending environmental danger would permit the safe occurrence of more sleep. In the oppossum, almost every REM period is followed by an arousal before the resumption of sleep. (Vestiges of this phenomenon appear in all mammalian sleep.) Under circumstances of environmental stress, the awakenings become lengthy and may even replace the REM period. Thus, early in mammalian evolution, REM sleep may have functioned to afford the organism the advantages of high levels of sleep by periodically permitting it to both monitor and respond to potentially threatening situations.

Predictions that follow from this theory include the fact animals and humans should display "critical reactivity" (differentiated and appropriate response to external conditions) (Snyder, 1969) after REM sleep awakenings as compared to NREM awakenings. Human data indicate that less confusion accompanies REM awakenings than those of Stages III

and IV, but not Stage II (Broughton, 1968). Monkeys have also been reported to appear more alert after REM (as compared to NREM) awakenings (Reite, 1965). Furthermore, Snyder suggests that the early morning awakenings reported to occur in depressive patients may reflect an analogous response to an internal danger signal. The sentinel hypothesis is disputed by the fact that, in cats, thresholds for awakenings are highest during REM sleep (for discussion of this issue, see Dement, 1966).

This theory would predict a non-monotonic relationship between the extent of danger to which a particular species as exposed at some critical point in history and the percent of sleep time spent in REM, since the most defenseless animals could not afford long sleep periods (for example, large and diurnal animals), and the least defenseless would not need the sentinel opportunity offered by the REM state. The amount of time spent searching for food would also be a factor determining REM percent, since those organisms that needed to be constantly engaged in food-seeking would not be able to take advantage of increased amounts of sleep. This, as Snyder points out, is teleological in that the organisms may need to eat more because they sleep so little. In addition, he suggests that this theory requires investigation of response to discriminable danger signals during various sleep and sleep deprivation conditions for further evaluation. According to Snyder, REM sleep may be a vestigial response to environmental conditions that no longer exist. One would not predict that modification of the sleep cycle would result in important behavioral consequences. The sentinel hypothesis offers a weak explanation for the REM rebound phenomenon.

Information Consolidation Theory. Due to the facts that: 1) REM sleep occurs predominantly in mammals (Snyder, 1969); and 2) REM

sleep is more prominent in neonatal and infant sleep (Roffwarg et al., 1966), it has been hypothesized that this state in some way facilitates acquisition, consolidation and/or storage of new information. Roffwarg and co-workers (1966) have hypothesized that during early life, maturational processes such as mylenization are facilitated by REM sleep. Stern (1971) and Fishbein (1970) have hypothesized that REM sleep optimizes the organism's capacity to acquire new information, and Fishbein (1971) has hypothesized that REM sleep is necessary for the conversion of information from short-term to long-term storage (see above for discussion of this theory).

Greenberg and Pearlman (1974) hypothesized that REM sleep is necessary for consolidation of newly acquired information resulting in behavior that is not species-typical. They explain the association of REM sleep to mammals by the fact that mammalian survival is dependent on behavioral adaptations and responses to environmental stimuli that are not pre-programmed. Thus, in contrast to Dement, they predict that performance of only behaviors dependent upon complex environmental stimuli will be impaired in response to REM deprivation.

The consensus of the literature investigating the effect of REM deprivation on retention lends support to this hypothesis (Albert et al., 1970; Greenberg et al., 1970, 1972; Holdstock & Verschoor, 1973; Joy & Prinz, 1969; Pearlman, 1973; Pearlman & Greenberg, 1973; Pearlman & Becker, 1974, 1975) (but see critique of methodology above). However, studies showing an enhancement of aggressive behavior (supposedly REM-independent) in response to REM deprivation suggest that this behavior may be facilitated by REM deprivation and that REM deprivation may affect behavior through alteration of something other than a consolida-

tion mechanism. Ellman and co-workers (1978) offer an alternative explanation of these findings (see above).

Drive-Reward Theory. Ellman and co-workers (1978) have hypothesized that a minimal level of neural activation is necessary to maintain behavioral responsivity. During waking, environmental stimuli are the source of this activation. During sleep, when sensory input and proprioceptive feedback signals are at a minimal level, the REM sleep state may serve to provide a source of endogenous stimulation. It has been hypothesized that ICSS reflects activation of drive and reward systems in the brain (see Deutsch & Howarth, 1963). Based on the finding that a reciprocal relationship exists between REM sleep and ICSS (Steiner & Ellman, 1972), Ellman and co-workers (1978) have hypothesized that REM sleep and specific motivated waking behaviors may be mediated by common reward mechanisms in the brain. Specifically, they have hypothesized that the ICSS neural circuit comprises part of the REM sleep network. This notion is supported by the finding that the locus coeruleus, a brain site believed to be an integral part of the REM sleep mechanism, supports ICSS behavior (Crow, 1973; Ellman, Farber, Mattiace, & Steiner, 1974).

Hypothalamic sites from which goal-directed behavior can be electrically elicited also support ICSS. These stimulus-bound behaviors have been shown to display many characteristics of motivated behavior (Coons, Levak, & Miller, 1965) (see below). As part of the ICSS network, these neural mediators of behavior may also be part of the REM sleep system. It therefore follows that REM deprivation should alter thresholds for elicitation of these behaviors. To the extent that "drive" as a unified concept affects all motivated behaviors similarly, it would be predicted that REM deprivation should lower thresholds for

all stimulus-bound behaviors. However, if REM deprivation (or ICSS) mimics an activated state such that some behaviors are facilitated while others are suppressed (this would be likely to aid in some adaptive function), then thresholds for specific stimulus-bound behaviors might be differentially affected by REM deprivation. An example of one such naturally occurring state is sympathetic nervous system activation which can be stimulated by threat of a predator (Keaton, 1967) or artificially by adrenalin or amphetamine administration (Schildkraut & Kety, 1967). This state facilitates behaviors such as aggression, but inhibits behaviors such as feeding. If REM sleep represents a manifestation of sympathetic nervous system activation, then stimulus-bound behaviors may be differentially affected by REM sleep deprivation. Specifically, aggression would be facilitated, while feeding would be inhibited in response to REM deprivation.

Feeding

Rats maintained on a free-feeding schedule such that food is easily accessible and in unlimited supply exhibit regular, patterned behavior. When faced with various metabolic or environmental challenges they exhibit predictable alterations in feeding patterns. Under standard laboratory conditions, feeding occurs in bursts of ingestion separated by periods of no eating. Depending on the criteria used to define a meal, rats ingest approximately 21.4 grams distributed among eight (Le Magnen & Tallon, 1966) to 12 (Balagura & Coscina, 1968) meals per day. Changes in feeding are usually effected thorugh alteration of meal size or meal frequency, but not both. Le Magnen (1972) reports that meal size is correlated with post-prandial, but not pre-prandial, inter-meal intervals. Rats alter meal size in response to food deprivation

(Levitsky, 1970), demands of lactation (Kissileff & Becker, 1974), caloric dilution (Snowdon, 1969), and taste (Levitsky, 1970). Meal frequency is altered in response to cold water stress (Kissileff, 1968).

In addition to a two to four-hour ultradian feeding cycle, rats show a marked circadian variation in amount of food ingested. Sixty-one percent (Le Magnen & Tallon, 1966) of the food eaten for a given day is consumed during the dark period if the animal is maintained on a light-12-hour, dark-12-hour (L-12, D-12) schedule. According to Le Magnen and Tallon (1966), the difference in light versus dark consumption is attributable solely to meal size; however, Balagura and Coscina (1968) report significantly more meals, and significantly larger meals, in the dark as compared to the light. Since in the latter study a shorter inter-meal interval defined a meal (30 vs. 40 minutes), it is possible that some of the discrepancy can be ascribed to the fact that food-taking occurs at 31 to 39 minutes after termination of what Balagura and Coscina define as a meal more frequently in the dark than in the light. When availability of food is made contingent upon a lever-press response on a continuous reinforcement schedule, the circadian distribution of feeding adheres to that of the ad libitum feeding schedule; however, under conditions in which demanding operant schedules are required to obtain food, or in response to food deprivation, lighting condition is not a salient stimulus. Alteration of diet palatability does not affect the circadian distribution of feeding (Levitsky, 1974).

Taste responsitivity has been shown to vary under different conditions of nutritional repletion. Traditionally, it was believed that animals tolerated poor taste more when they were hungry than when

satiated. The finding that rats tolerated higher levels of quinine adulteration in a milk diet if they were food deprived lend support to that notion (Miller, 1956). Jacobs and Sharma (1969) have hypothesized that taste responsivity is enhanced during food deprivation conditions. They suggest that in Miller's study, rats tolerated more quinine not because of decreased avoidance of a negative stimulus (Tenen & Miller, 1964), but rather because of an increased approach response towards the palatable milk substance. They reported that hungry, but not normal, rats tolerate less quinine adulteration of corn syrup than of an isocaloric glucose solution. The facts that: 1) animals prefer saccharin to glucose solutions under conditions of caloric deprivation (Sheffield & Roby, 1950); 2) animals will starve rather than ingest food that is highly adulterated (Kennedy, 1950); and 3) introduction of food directly into the stomach does not fully substitute for orally ingested food (Berkun, Kessen, & Miller, 1952) according to measures of food ingestion, stress the importance of the modulatory influence of taste variables on feeding.

A. Neurophysiology

Hypothalamic catecholamine mechanisms have been investigated extensively with regard to their role in feeding regulation through neuroanatomical and neurochemical lesion and stimulation of both hypothalamic areas and of more caudal brain sites that are believed to innervate the hypothalamus.

Lesions in the area of the lateral hypothalamus result in a behavioral syndrome characterized by aphagia and adipsia (Anand & Brobeck, 1951; Teitelbaum, 1961). If animals are force-fed, they recover eating behavior over a period of 90 days; however, water regula-

tion never reaches normal levels. Conversely, lesions in the area of the ventromedial hypothalamus result in overeating, raised levels of body weight regulation and highly taste-responsive feeding (Teitelbaum, 1961; Teitelbaum & Campbell, 1958). Recently, the obesity syndrome has been linked to lesions of fibers of the ventral noradrenergic bundle (Ungerstedt, 1971) passing through the area of the ventromedial nucleus of the hypothalamus (Gold, 1973; Ahlskog, Randall, & Hoebel, 1975; Sclafani, Berner, & Maul, 1975).

Based mostly on lesion studies and on electrical stimulation studies (see below), early investigators concluded that the lateral hypothalamus controlled hunger (Teitelbaum, 1961). More recent studies showing sensory and motor deficits (possibly due to inadvertent lesions of the trigeminal nerve) (Zeigler, 1974) caution against invoking premature motivational concepts. Similarly, the obesity syndrome was attributed to changes in body weight set point (Teitelbaum, 1961), satiety (Miller, 1960), affective state (Grossman, 1966), and lipostats (Sclafani & Kluge, 1975), but is more recently being discussed in terms of metabolic substances and their communication with the brain (Friedman & Stricker, 1976; Powley, 1977).

Electrical stimulation of the ventromedial hypothalamus results in a suppression of feeding in hungry rats (Krasne, 1962; Wyrwicka & Dobrzecka, 1960), and stimulation of the lateral hypothalamus elicits feeding in satiated rats (Anand & Dua, 1955). Electrically elicited feeding occurs at reliable current intensities within a subject, and has been the focus of a good deal of investigation. It should be noted that electrical stimulation of the hypothalamus has been reported to elicit copulatory behavior (Caggiula, 1970) and a rage response (in the

cat) (Flynn, Edwards & Bendler, 1971; Miller 1961). Specifically, these responses are associated with stimulation of the posterior hypothalamus and anterior hypothalamus respectively; however, mapping studies have failed to delineate areas that either reliably elicit or exclude elicitation of any particular response (Valenstein, 1970). This electrically-elicited feeding response, known as stimulus-bound eating (SBE), is defined as a goal-directed response, i.e., the response occurs only in the presence of an appropriate goal object (food) and can be modified if conditions for attaining the goal object are altered.

Another line of support for the notion that the response reflects a motivated state lies in the fact that in almost all cases examined, brain sites that mediate stimulus-bound behaviors also support ICSS (Margules & Olds, 1962). At SBE electrode sites, self-stimulation behavior is enhanced by food deprivation (but not sex hormone manipulation) (Gallistel & Beagly, 1971) or by the presence of food on the response lever (Coons & Cruce, 1968). In brain sites known to support stimulus-bound copulatory behavior, the presence of an estrus female enhances ICSS rates (Caggiula & Hoebel, 1966). Mendelson (1967) has elaborated on the notion that excitation of stimulus-bound behavior sites creates a drive, and that consumption of the goal object is rewarding. Rather, he suggests that the combination of the stimulation and the goal object is rewarding. He found that rats that exhibited stimulus-bound drinking behavior would emit a lever-press response to administer stimulation of stimulus-bound drinking brain sites only if water was present. Thus, the combination of thirst and water was reinforcing. Ellman and Steiner (1973) have hypothesized that ICSS sites

form a neural network that fires in association with drive and reinforcement, and that brain sites supporting stimulus-bound behaviors are sub-systems of the ICSS network which fire in association with reinforcement of specific behaviors.

Valenstein (1970) hypothesizes that stimulus-bound behaviors reflect the activation of neural substrates of species-specific behaviors (known as fixed action patterns) rather than a "biological need" state. He suggests that feedback associated with the execution of these behaviors provides the reinforcement associated with stimulus-bound behaviors. He reasons that in the case of SBE, since food and stimulation is more reinforcing than stimulation alone, the stimulation cannot excite all of the reinforcement associated with feeding. This position is supported by the fact that several non-consummatory stimulus-bound behaviors such as grooming and food-carrying can be elicited from electrical stimulation of the hypothalamus (Valenstein, 1968). Flynn and co-workers (1971) have shown that, in cats, the hypothalamically elicited attack response is mediated at least partially through facilitation of specific sensory and motor systems, and that in the presence of an appropriate goal object, overt behavior is affected.

Valenstein hypothesized that the neural system mediating stimulus-bound behaviors is "plastic." That is, the same neurons are capable of mediating several behaviors and the particular behavior elicited by the stimulation is dependent on the animal's prior experience of associating the stimulation and the goal object. He has demonstrated that by varying the goal objects present in the testing situations, he can elicit different goal-directed behaviors in response to the same stimulation. Additional support for his hypothesis rests with

the fact that stimulus-bound behaviors are frequently dependent upon characteristics of the goal object other than those inherent in its consummatory value. He cites the fact that by changing the shape of the food dish, he can abolish SBE. Additionally, mapping studies have failed to localize specific sites for elicitation of different behaviors (Valenstein, 1970).

A contrasting hypothesis with regard to "site-specificity" has been suggested by Wise (1968), who proposed the existence of two interwoven but fixed neural systems mediating stimulus-bound feeding and drinking. He reported that stimulation to an electrode site supporting stimulus-bound behavior results in a gradual lowering of threshold for that behavior with repeated stimulation over time. Thus, Valenstein's finding that stimulation of an electrode site can elicit several behaviors can be attributed to the interactive effects of current spread and lowering thresholds for elicitation of specific behaviors. Wise's inference gains support from a study by Olds, Allan and Breese (1971) in which they were able to localize discrete and differential sites for SBE, elicited drinking, and rewarding brain stimulation through the use of small probes and low current levels. In addition, the findings that drug manipulations can differentially affect stimulus-bound feeding and drinking behaviors support this notion (Grossman, 1960).

B. Neurochemistry

Injections of norepinephrine (NE) to the hypothalamus have been found to elicit feeding in satiated rats (Grossman, 1962; Leibowitz, 1974; Miller, Gollesman & Emery, 1964). Mapping studies indicate that extra-hypothalamic injections do not elicit this response and that the most sensitive area within the hypothalamus is the paraventricular

nucleus (Leibowitz, 1973). Leibowitz (1975b, 1978a) has provided evidence that the feeding response is due to activation of catecholamine (CA) receptors by demonstrating a dose-dependent effect with injections of exogenous CA and drugs known to release endogenous CA (such as amphetamine), and drugs that increase synaptic availability of CA by blocking reuptake (such as amitriptyline, protriptyline, and desimipramine). In addition, by suppressing the response through use of alpha-adrenergic receptor blockers such as phentolamine, but not beta-adrenergic, cholinergic or dopaminergic receptor blockers, she has demonstrated that this response is mediated through alpha-adrenergic receptor sites in the area of the paraventricular neucleus (Leibowitz, 1975b, 1978b).

Thus, CA-elicited feeding resembles the normal feeding response in magnitude, and furthermore, it occurs in a temporal sequence of responses (including preprandial drinking and diuresis, grooming and searching) similar to that of normal feeding (Leibowitz, 1975a). There is preliminary evidence suggesting that this response is associated with the sensory qualities (Sorensen, Ellison, & Masuoka, 1972; Booth & Quartermain, 1965) or rewarding aspects of feeding (Ritter, Wise, & Stein, 1975).

In addition to an alpha adrenergic receptor mechanism mediating the feeding response, Leibowitz has defined beta adrenergic and dopaminergic receptor sites in the area of the perifornical lateral hypothalamus that exert a suppressive influence on feeding. Mapping studies similar to those described for the alpha adrenergic feeding mechanism have been conducted. The sites have been defined chemically through CA agonist and antagonist injections to the specific hypo-

thalamic sites (Leibowitz, 1977).

Margules (1970a, 1970b) has reported that both alpha and beta adrenergic agonists injected into the hypothalamus result in a suppression of feeding. He utilized doses which were considerably higher than those used by Leibowitz. In addition, he has not conducted extensive mapping studies that would lead to neuroanatomical localization of these sensitive areas. Margules suggested that the alpha and beta adrenergic inhibitory mechanisms which he is activating are responsive to distinct satiety cues. He showed that alpha adrenergic activation or beta adrenergic deactivation resulted in inhibition of feeding in response to internal satiety cues, whereas beta adrenergic activation or alpha adrenergic deactivation resulted in an inhibition in response to the sensory qualities of food. In a later study aimed at accounting for the discrepancy between his data and that of Leibowitz, he found that central NE injections at three hours after the onset of the dark period (in animals maintained in L-12, D-12 lighting conditions) suppressed feeding, while identical injections administered at 1 1/2 hours after the onset of the light period resulted in enhanced feeding (Margules, Lewis, Dragovich, & Margules, 1972). Margules suggested that eating occurs when hypothalamic NE reaches some optimal level and that adding NE in the light raises NE to that level, while adding NE in the dark moves it further from the criterion level at which feeding is most likely to occur. Leibowitz (1976) has reported that no time-of-day differences exist for the injections she reports.

Although the neurochemical substrate(s) of electrically elicited feeding is unknown, the possibility that brain CA may play a role in this phenomenon has been suggested by a few studies which have shown

that drugs that alter brain CA activity influence the elicited feeding response. Specifically, peripherally injected amphetamine (Miller, 1960; Stark & Totty, 1967; Wisehart & Walls, 1974) and phenylpropanolamine (Hoebel, Hernandez & Thompson, 1975), drugs known to enhance CA receptor action, have been found to inhibit electrically elicited feeding. A similar effect has been reported for peripheral injection of the dopaminergic blocker, haloperidol (Philips & Nikaido, 1975) and central injection of 6-OHDA (Philips & Fibiger, 1973), a drug that destroys CA terminals. Both drugs result in a decrease of CA receptor activity. Thus, while these studies have established a link between brain CA and electrically elicited behavior, the nature of this association, the level at which it occurs, and the brain areas involved, remains unclear.

More caudal brain areas have been investigated in regard to their regulatory effect on eating, since it is believed that brainstem mechanisms innervate many hypothalamic sites. Gold (1972) initially reported that the well-known obesity syndrome results from lesions of the ventral noradrenergic bundle rather than the ventromedial nucleus of the hypothalamus. Ahlskog, Randall and Hoebel (1975) have shown that ventral bundle lesions and medial hypothalamic lesions result in additive obesity syndromes. Hypothalamic lesions result in more overeating, disruption of circadian feeding cylce and finickiness. Ventral bundle lesions result in less overeating and greater forebrain depletions of NE, but preservation of normal taste responsivity. Ahlskog (1974) reported that midbrain lesions (using either electrolytic or 6-hydroxydopamine lesions) of the ventral bundle, but not the dorsal bundle, cause obesity, NE depletion in the forebrain, and attenuation

of the anorexic effect of amphetamine.

Leibowitz and Brown (1978a, b) have reported that electrolytic and 6-hydroxydopamine lesions of the midbrain dorsal tegmentum abolish CA elicited feeding in the paraventricular nucleus, and that lesions of the midbrain ventral tegmentum abolish CA-induced suppression of feeding in the perifornical lateral hypothalamus. They have shown through fluorescence microscopy that these lesioned brain sites innervate the paraventricular and perifornical areas respectively. Jones and Moore (1977), using audioradiographic techniques, have shown that the locus coeruleus innervates the paraventricular nucleus in cats. However, studies investigating feeding in response to locus coeruleus lesions in cats (Jones et al., 1977) and rats (Osumi, 1975) have reported no changes in feeding. Halperin, Halperin, Pollens, and Pavlides (1978) have reported a hyperphagic response to dorsal brainstem lesions. This response differs from the hypothalamic hyperphagic syndrome according to various motivational measures. Histological analyses are in preliminary stages in this study.

Feeding has been electrically elicited from brain sites caudal to the hypothalamus along the path of the medial forebrain bundle caudally to the ventral tegmental area of Tsai (Walldbillig, 1975) and into the pontine tegmentum involving areas such as the locus coeruleus, superior cerebellar peduncles, and the mesencephalic nucleus of the 5th cranial nerve (Micco, 1974). This extrahypothalamic feeding response is not associated with exploratory behavior (Micco, 1974). In fact, the food must be placed in the animal's sensory field in order for the behavior to occur. It should be noted, however, that removal of the food during stimulation results in the cessation of mastication. This

demonstrates the importance of sensory input for the feeding response associated with midbrain and hindbrain stimulation.

Amphetamine

A. Neuropharmacological Effects

Amphetamine's action is that of an indirect acting sympathomimetic amine in the peripheral adrenergic nervous system. That is, it mimics the effects of NE by displacing the amine in the nerve ending. Similarly, in the central nervous system, amphetamine acts through displacement of NE at the nerve terminals. Centrally, amphetamine also causes release of dopamine (DA) (through displacement), inhibits uptake of NE and DA, and blocks metabolism of NE and DA by inhibiting monoamine oxidase. Both the d- and the l- isomers exert these effects. The release of catecholamines resulting from amphetamine administration is generally not sufficient to reduce normal brain levels of these substances because of rapid resynthesis (Iversen & Iversen, 1975).

B. Behavioral Effects

Behaviorally, amphetamine acts as a stimulant and an anorexic agent. In both regards, the d- isomer is more potent that the l- isomer. That pre-treatment with alpha-methyl paratyrosine abolishes the behavioral effects of amphetamine lends support to the hypothesis that displaced catecholamines mediate these effects. In addition, chlorpromazine, which blocks central NE and DA receptor sites, antagonizes the behavioral effects of amphetamine (Iversen & Iversen, 1975).

Amphetamine has been found to increase arousal, stimulate spontaneous motor behavior, enhance learning, selectively suppress REM sleep, and, in some cases to disrupt beahvior. Eating is inhibited, although conditioned responses associated with food reward are enhanced

(Iversen & Iversen, 1975).

It is necessary, when evaluating the effects of amphetamine, to be precise as to the specific behavior that is affected. Inferences must be carefully proposed. For example, enhancement of behavior with a low baseline level is generally greater than enhancement of behavior with a high baseline level (Dews, 1958). Steiner & Stokely (1973) report that the inverted U-shaped rate intensity curve typically observed with hypothalamic ICSS behavior is preserved but shifted in the direction of lower current intensities. Thus, at most stimulation intensities lever-pressing rates are increased; however, at some intensities rates are suppressed. In addition, behavioral effects are dependent upon response compatability (Lyon & Randrup, 1972). Malmo (1959) has suggested that a U-shaped function describes the relationship between arousal and behavioral efficiency. Amphetamine has been shown to alter the same behavior in opposite directions by varying dose level (Lyon & Randrup, 1972).

The facilitatory effects of amphetamine on learning have been demonstrated through shock avoidance tasks. Poor learners show greater facilitation than good learners. Dews (1955) reported that behavior was maintained by amphetamine during simple S^D/S^Δ conditions, but disrupted during complex S^D/S^Δ conditions. Amphetamine has been reported to disrupt behavior on a differential reinforcement of low rates schedule and, in monkeys, to disrupt performance on a visual matching task.

Amphetamine has been found to enhance ICSS when electrode sites are in the medial forebrain bundle (Stein, 1965). Carlsson (1966) has shown that amphetamine in this area causes release of NE from

terminals. In addition, spiroperidol suppresses ICSS in the medial forebrain bundle. It has been suggested (Warburton, 1977) that dopamine pathways originating in the interpenduncular nucleus may mediate the motor effects of amphetamine on ICSS, while NE pathways originating in the locus coeruleus may mediate its enhancement of reward. This notion gains support from the finding (Ellman, Ackermann, Bodnar, Jackler, & Steiner, 1976) that d-amphetamine enhances ICSS more than l-amphetamine in dorsal brainstem and hypothalamic sites. In addition, mid-ventral tegmental ICSS sites are not differentially affected by d- versus l-amphetamine.

Hypothesis

Evidence suggests that neural systems involved in the mediation of waking behaviors are also activated during REM sleep. Cortical neurons exhibit firing patterns during REM sleep that are similar to waking patterns, but dissimilar to discharge activity during NREM sleep. Dement (1969) has suggested that REM sleep serves as a period during which the central nervous system areas involved in the mediation of motivated behaviors are activated even though there is enforced muscle atonia (i.e., active inhibition of many major muscle groups). It has been reported that cats lesioned in caudal aspects of the locus coeruleus fail to exhibit muscle atonia during REM sleep (Jouvet, 1973). These cats often display appetative or consumatory behaviors related to feeding or aggression (in the absence of any external stimuli) during REM sleep. In addition, PGO spikes, normally associated with REM sleep, are associated with stereotypic drive behaviors when they occur during waking. Dement has hypothesized that all motivated behaviors (those resulting in feeding, drinking, copulation, or aggression) are

energized by a unitary drive system, and that the "pressure" of this system is regulated by the REM sleep mechanism. According to this notion, REM sleep is a manifestation of excess drive energy. In addition, Dement hypothesized that as a means of dissipating drive energy, the occurrence of REM sleep may be interchangeable with waking drive behaviors. This hypothesis would predict a lowering of thresholds for all waking motivated behaviors in response to REM deprivation.

Other investigators have suggested that REM is a state that prepares the organism for learning (Hartmann & Stern, 1972; Greenberg & Pearlman, 1974), or a state during which memory consolidation occurs (Greenberg & Pearlman, 1974; Fishbein, 1970, 1971). Greenberg and Pearlman hypothesized that consolidation of complex behaviors, rather than species-specific behaviors, occurs during REM sleep.

Studies investigating the effects of REM deprivation on motivated behaviors have reported enhanced aggression, lowered thresholds for ICSS behavior, and inhibition in consolidation of complex tasks; however, there is a paucity of data suggesting that REM deprivation enhances feeding behavior.

There is evidence that NE is intimately involved in the regulation of REM sleep (Jouvet, 1969b). Amphetamine, a sympathomimetic drug that produces a variety of behavioral changes (Schildkraut & Kety, 1967), is known to exert these effects through increased synaptic availability of NE (Iversen & Iversen, 1975). Behavioral alterations associated with amphetamine administrations include increased activity (Taylor & Snyder, 1971), inhibition of REM sleep (Rechtschaffen & Maron, 1964), enhanced aggression behavior (Lal, Nesson & Smith, 1970), and suppressed feeding response (see Iversen & Iversen, 1975). Amphetamine also facilitates

learning of simple tasks while interfering with learing of complex tasks (Dews, 1955; McGaugh & Petrinovich, 1965).

Furthermore, amphetamine exerts a paradoxical effect upon ICSS and stimulus-bound eating behavior elicited from the same electrode in that ICSS thresholds are lowered, while stimulus-bound eating thresholds are elevated following amphetamine administration (Miller, 1960). Thus, the effect of amphetamine on motivated behavior is not uniform, but rather differential with respect to specific behavior.

REM deprivation and amphetamine administration have many similar behavioral effects. As already noted, both treatments increase spontaneous motor activity (Albert et al., 1970; Taylor & Snyder, 1971), increase various measures of aggression (Lal, Nesson & Smith, 1970; Morden et al., 1968; Sloan, 1972), and facilitate the acquisition of simple tasks (Greenberg & Pearlman, 1974; McGaugh & Petrinovich, 1965) and enhance ICSS (Steiner & Ellman, 1972). In humans, clinical improvement of endogenous depression has been reported in response to both REM derpivation (Vogel et al., 1968) and amphetamine (Goodman & Gilman, 1955).

It is hypothesized here that REM deprivation may activate behavioral mechanisms similar to those stimulated by amphetamine administration. This includes sympathetic neural activation, known to serve as an adaptive response to predatory challenges. REM deprivation is reported to occur naturally during conditions of predatory stress (see Snyder, 1969). Thus, REM deprivation may serve as a mechanism that energizes sympathetic activation during conditions of environmental challenge.

Sympathetic nervous system activation is associated with inhibi-

tion of intestinal peristalsis, and decreased blood flow to the digestive tract, and may, therefore, suppress feeding. If REM deprivation exerts influence on behavior through sympathetic activation, it may also suppress feeding behavior.

This experiment was designed to explore the relationship of eating, a waking motivated behavior, to REM sleep through the use of stimulus-bound eating which is believed to reflect some aspects of motivated feeding behavior and some aspects of stereotypic feeding behavior. If the similarities noted between amphetamine and REM deprivation occur across other motivated behaviors, then stimulus-bound eating thresholds should be elevated in response to REM deprivation. This is contrary to Dement's (1969) hypothesis that REM deprivation lowers thresholds for all motivated behaviors. This prediction is also contradictory to the hypothesis that REM deprivation does not affect species-typical behaviors (Greenberg & Pearlman, 1974).

Margules and co-workers (1972) reported opposite effects of hypothalamic NE injections on feeding behavior at two different points in the light/dark cycle in rats. If REM deprivation exerts its effect by altering hypothalamic NE levels, then REM deprivation may have differential effects on stimulus-bound eating at different points in the circadian cycle.

The following experiments comprise a systematic attempt to determine the effects of REM deprivation on stimulus-bound eating thresholds. These effects were measured at the two points in the light/dark cycle where Margules observed opposite effects of NE injections on feeding behavior. Two different sets of stimulation contingency conditions

were utilized. Finally, strict controls for the nonspecific effects of stress upon stimulus-bound eating were maintained.

METHOD

Subjects

The subjects were Holtzman male, albino, Sprague-Dawley rats weighing approximately 250 gms upon arrival. The animals were housed individually or in pairs in 18 x 42 x 20 cm Plexiglas cages covered with wire mesh. All subjects were maintained on Teklad mouse pellets and water available ad libitum, in a room with a relatively constant temperature of approximately 68°F.

Housing was under one of two sets of 12-hours lights on, 12-hours lights off (L-12, D-12) conditions. For one group of subjects, the lights turned off at 7:00 a.m. and on at 7:00 p.m. For the second group, lights turned off at 12:30 p.m. and turned on at 12:30 a.m.

Surgical procedures were performed when the subjects weighed 420-500 gms. Subsequent to surgery, all animals were housed individually. Sixty-nine (69) subjects underwent surgical procedures; 16 subjects were utilized for the experiment.

Surgical Procedure

Each subject was implanted with a stimulating electrode and electrodes for recording electroencephalograph (EEG) and electromyograph (EMG).

Animals were anesthetized using either Chlorapent (2.1 mg/kg) or Sodium Thiopental (1.3 mg/kg), injected intraperitoneally, and ether. Supplementary injections of approximately five to ten percent of the initial dosages were administered whenever necessary.

The surgical procedure consisted of placing the animal in a Kopf stereotaxic device, exposing the skull, and drilling 1.3 mm diameter holes in the skull through which the electrodes were implanted.

Stainless steel, bipolar electrodes (MS303/1, Plastic Products Company) were used as stimulating electrodes. Each electrode consisted of two wires, insulated except at the tips. The diameter of each tip was 0.35 mm and the distance between the tips was 0.24 mm. The electrode was cut to a length of 9 mm and, with the use of a stereotaxic instrument, was aimed at the left lateral hypothalamus. With the incisor bar set at -5, the coordinates used were the midpoint between lambda and bregma, 1.7 mm left of the sagittal suture, and 8.5 mm below the surface of the skull.

Stainless steel screws, 1.0 mm in diameter and 4.5 mm long, were screwed into the right side of the skull to record EEG. The posterior screw was placed approximately midway between lambda and bregma and one to two mm to the right of the midline suture. The anterior screw was placed approximately 3.0 mm anterior to bregma and 4.0 mm lateral to the midline suture. One of the two wires of an electrode (MS303/1, Plastic Products Company) with insulation removed, was tied to each screw.

Bipolar subcutaneous electrodes (MS303/71, Plastic Products Company) were used to record EMG. Each electrode consisted of two stainless steel wires, 0.125 mm in diameter, coiled into a spring with six turns per mm. The diameter of each spring was 0.5 mm. Each spring was insulated with polyethylene tubing except for approximately 7.0 mm at the tips, where the insulation was removed. The trapezeus muscle was exposed and separated. One of the two wires of the subcutaneous electrode was tied to the left and right levator scapulae and the trapezeus was sutured back together.

After implantation, the electrodes were fixed into place with an

acrylic cement anchored to the skull with stainless steel screws. A one-week to one-month recovery period followed the surgical procedure.

Threshold Assessment

Each animal was run at the same time each day, through a stimulation session in which an electrical threshold for SBE was determined. The subject was weighed, attached to a lead, and placed in a 20 x 23 x 21 cm testing chamber that contained a dish of Purina lab chow mixed with water. The animal was left undisturbed for 25 minutes, at which time his chamber was moved to the location of the stimulation apparatus. The subject was again left undisturbed for five minutes. At this point, the stimulation session began. During the actual experiment, all animals were handled with gloves.

Throughout all testing procedures, consecutive trials consisting of 30 seconds of continuous sinusoidal wave current were delivered with intertrial intervals of 30 seconds. A trial was rated as positive if the animal initiated feeding at any time during the trial, and negative if no feeding occurred during the trial. Feeding was defined as the ingestion and swallowing of food obtained from the dish. A trial was discounted if the subject ate during the four seconds preceding the onset of the trial.

Screening. All animals were screened for a feeding response to electrical stimulation. Animals were screened in 20-30 trial sessions in which the current intensity of the stimulation was varied from 5 mv to 40 mv, focusing on those intensities at which the subject displayed exploratory, activated or feeding related behaviors such as sniffing, mastication and grooming. Subjects not displaying SBE behavior after approximately 15 testing sessions were eliminated from the experiment.

Subjects were classified as stimulus-bound eaters if they reliably displayed a feeding response over a consistent range of current intensities for five days.

Each animal's SBE threshold was determined through the use of one of two threshold assessment procedures: R-50 or multiple ascending.

R-50. In this procedure, the subject was run in consecutive blocks of five trials in which the stimulation intensity varied between blocks. The testing session was terminated when a threshold was obtained. During one randomly selected trial of each block, no stimulation was presented (a blank trial) to verify satiation. The remaining four trials of the block were run identically to each other in stimulation intensity. If a trial was discounted, an additional trial was run at that intensity. Thus, a block of trials always consisted of a blank trial and four non-discounted stimulation trials.

The first block of trials was run at two mv below the previous day's threshold. If the animal initiated eating during fewer than 50% of the trials, the current intensity of the next block of trials was incremented by one mv. This method was continued until the animal ate during at least 50% of the trials within a block (at least two of the four non-blank and non-discounted trials), which terminated the daily stimulation session.

If, during the first block of trials, the rat initiated eating during 50% of the trials or more, then the next block of trials was run at one mv below the starting intensity. Successive blocks of trials descended by one mv until the animal ate during fewer than 50% of the trials in a block, which terminated the daily stimulation session.

A threshold was assessed for each daily stimulation session. The

threshold was defined as the intensity at which the animal ate 50% of the time. If the animal did not eat precisely 50% of the time during any block of trials, the threshold was extrapolated through linear interpolation. If the animal ate exactly 50% of the time during one, and only one block of trials, the stimulation intensity of that block was designated as the threshold. If the animal ate exactly 50% of the time during two or more blocks of trials, then the intensity of the block with the lowest stimulation level was designated as the threshold.

Multiple Ascending. The subject was run through four consecutive blocks of five trials each. Within each block, the stimulation intensity of each trial was set at three mv above that of the previous trial. Thus, each block of trials spanned a range of 12 mv.

The first trial of the first block was run at six mv below the previous day's threshold. The first trial of the second block was run at either one mv above or below the intensity of the first trial of the first block. The first trial of the third block was run at either one mv above or one mv below the first trial of the first block, whichever was not run during the first trial of the second block. The fourth block was identical to the first block. Thus, the 20-trial stimulation session spanned a range of 14 mv and had a median intensity equivalent to the previous day's threshold.

A threshold was determined for each block of trials. In the case where the animal initiated feeding during all the trials in a block, the threshold for the block was designated as 1.5 mv below the lowest intensity in that block. If the animal initiated feeding during none of the trials in a given block, then the threshold was designated as 1.5 mv above the highest intensity in that block. If the animal

initiated feeding at some intensities in a block and not others, and if all the intensities at which eating was initiated were higher than all those intensities at which feeding was not initiated, then the threshold was determined as the midpoint between the lowest intensity at which eating occurred and the highest intensity at which feeding did not occur. If feeding occurred during two consecutive trials, and if no feeding occurred at any lower intensity, then the block threshold was determined as the midpoint of the lowest of those two trial intensities and the preceding trial intensity. In the case in which a positive trial occurred and was followed by a negative trial, or in the case in which a positive trial was discounted, then the trial was considered above threshold if, and only if, at least one of the corresponding trials in the other three blocks of trials was positive. In that case, the threshold of the block was determined as the midpoint between that trial and the trial immediately preceding it.

The threshold for the stimulation session was determined as the mean of the thresholds obtained for each of the four blocks of trials.

Platform Treatment

Animals were housed individually in 12 x 42 x 20 cm Plexiglas cages covered with metal grating that contained a food well and water bottle. A Plexiglas wall hung from the middle of the food well to about 0.64 cm off the floor of the cage. Thus, the animal could occupy only an 18 x 27 x 20 cm area. An inverted clay flowepot saucer was glued to the center of the floor of the cage. A circular Plexiglas platform 0.64 cm thick was screwed to the saucer. The platform stood 3.6 cm off the floor of the cage. The cage contained water to 0.32 cm from the top of the platform. Thus an animal housed in such apparatus

could stay dry only by standing on the platform.

During the REM deprivation condition, 7-15 cm diameter platforms were used; during the stress control condition, 15-17 cm diameter platforms were used. The platform diameters were selected so that when the subject experienced muscle atonia, i.e., during REM sleep, they were unable to maintain their position on the smaller sized platform. However, on the larger sized platform, there was sufficient area for the rat to remain on the platform even during periods of muscle atonia. Two to three days were frequently necessary for the rats to learn to maintain their positions on the larger platforms in the presence of muscle atonia.

Polygraphic Recording

Throughout the duration of the experiment, each subject was continuously connected to a Grass polygraph (model 7D) through a swivel which allowed free movement. Both the subject and the metal grating on the cage were grounded. All recordings were AC.

The polygraph was calibrated so that a 50 uV signal resulted in a one cm pen deflection. Each subject was recorded on two channels of the polygraph. The EEG channel recorded waves ranging from one to 35 Hz at full amplitude; the EMG channel recorded waves ranging from 10-75 Hz at full amplitude.

Polygraphic data was recorded on paper moving at five mm per second and was scored in 30-second epochs. Each 30-second epoch was divided into five equal periods (six seconds) and each period was divided into five equal divisions (1.2 seconds).

All scoring time fell into one of four categories: awake; slow wave sleep; REM sleep; unscorable (only 2.9% of recording time was

unscorable). Each epoch was scored as the stage that occurred during three of its five periods. A period was designated as whatever stage occurred during three of its five divisions. In the case in which three periods of a single stage did not appear in an epoch, the epoch was first scored as "mixed." Periods of REM were subtracted out and added to REM sleep time. The remaining "mixed" time was divided equally between awake and SWS. In addition, all occurrences of REM sleep were noted by designating the number of periods (at least three out of five divisions) of REM time (0-2). These periods were also subtracted from time in the sleep stage in which they occurred and added to REM sleep time. Thus, all scoring time reduced to Awake, SWS, REM, and unscorable.

Sleep Stage Criteria. Polygraphic data was scored in accordance with the criteria used by Fishman and Roffwarg (1970). A brief description of the seep stage criteria follows:

Awake: Characterized by low amplitude, high frequency EEG with theta activity frequently interspersed, in conjunction with a tonic EMG.

SWS: Characterized by high amplitude (distinguishable from awake) low frequency EEG.

REM Sleep: Characterized by a consistent theta rhythm in the EEG, in the presence of muscle atonia.

Drug Administration

Nine subjects were injected intraperitoneally with 2 mg/kg of d-amphetamine 20 minutes prior to the SBE threshold test for two consecutive days. Drug days were preceded and followed by two to three days of saline injections. D-amphetamine was dissolved in a 0.9% saline solution at a concentration of 2 mg/ml. Saline injections were at

volumes of 2 ml/kg.

Histology

After completion of the experimental procedure, subjects were overdosed with sodium thiopental or chloropent and perfused through the heart with a 10% formalin solution. The brain was frozen and cut into 40 μ thick coronal sections. Sections were stained with cresyl violet and luxol fast blue according to the method of Kluver and Barrera (see Wolf & Yen, 1968).

Electrode placements were localized according to Konig and Klippel (1963). During localization of electrode sites, the slides were coded so that the experimenter was unaware of the behavioral data for the animal whose slide was being analyzed.

Protocol

Subjects were housed under one of the two lighting conditions immediately or shortly after arrival at the laboratory. After surgery and a one-week to one-month recovery period, animals were screened for SBE behavior. Animals were tested for 15-25 sessions frequently interrupted by one to three-week intervals of no testing. Animals displaying reliable SBE behavior were tested for a SBE threshold each day at the same time until the completion of the experiment.

All testing occurred between 9:30 a.m. and 12:30 p.m. Thus, for the animals housed in the L-12:30 a.m., D-12:30 p.m. condition, testing occurred 9 1/2 to 11 1/2 hours after the onset of the light period (L-rats). For the animals housed in L-7:00 p.m., D-7:00 a.m. lighting conditions, testing occurred 2 1/2 to 5 1/2 hours after the onset of the dark period (D-rats).

When the subjects displayed stable SBE thresholds for five to

eight consecutive days, the experimental procedure began. Animals were attached to recording leads at all times through two days of adaptation (A), five days of baseline (BL), five days of either REM deprivation or large platform stress control (LP), and five days of recovery (R). There was some question as to the efficacy of the treatment in five subjects and therefore four subjects were administered an additional day of LP treatment, and one subject was administered an additional day of RD treatment. During A, BL, and R conditions, animals were housed in cages identical to those used in the REM deprivation and LP conditions, except that instead of containing a platform and water, these cages contained sawdust. Approximately two weeks after the termination of the R condition, the entire paradigm was run again, this time utilizing the platform condition (REM deprivation or LP) not previously run. For half the subjects, polygraphic data was recorded during BL, REM deprivation, LP, and R conditions. For the other half, polygraphic data was recorded for the same two out of every four hours each day.

During A, BL, LP, REM deprivation, and R conditions, animals were handled with gloves and weighed daily before the ad libitum feeding period preceding the threshold testing session. Each rat was run in the same testing chamber each day. All housing cages were cleaned daily while the subject was being tested for SBE threshold.

After completion of the last recovery day, the animals were disconnected from the polygraph. Nine subjects were maintained in the same housing and tested for SBE thresholds for six to eight additional days during which d-amphetamine or saline was administered 20 minutes before the testing session began. Subjects were administered two to three

days of saline followed by two days of drug, and two to three days of recovery (saline).

Upon completion of the experiment, animals were sacrificed and histological procedures were conducted. The polygraphic data was analyzed to verify the treatments.

Design. Half the subjects in each lighting condition were run in each threshold assessment procedure (see Figure 1). Thus, four subjects were run in each threshold/lighting subgroup of the experiment. Three of the four L-rats run in the R-50 condition were run in the REM deprivation condition before the LP condition. All four of the L-rats run in the multiple ascending condition were run in the REM deprivation condition prior to the LP condition. Two of the D-rats run in the R-50 condition were run in the REM deprivation condition prior to the LP condition, and two of the D-rats run in the multiple ascending condition were run in the REM deprivation condition prior to the LP condition.

RESULTS

Since small samples were used and data did not approximate a normal distribution, most changes in SBE thresholds, sleep-wake behavior and body weight across conditions were assessed through use of the Wilcoxen T test. In some cases, where deviation from normality was less extreme, t-tests for correlated means were used.

Thresholds during each platform condition were assessed by calculating the mean threshold for the fourth and fifth RD or LP days. (For three of the four rats run for an additional day of LP treatment, the fifth and sixth platform days were used in place of the fourth and fifth days.) Polygraphic data assessing sleep in conjunction with use of the inverted flower-pot technique suggest that during these days, RD treatment is most selective in its REM sleep deprivation effects (see Vogel, 1974).

Description of Treatment

A. Electrode Placement

Six of the eight L-rats had electrode tips placed in the medial forebrain bundle (see Figure 2). For one rat, electrode tips bordered the fornix, close to the medial forebrain bundle (see Figure 3), and one rat had tips localized in the H_2 Field of Forel (see Figure 4).

Four of the eight D-rats had electrode tips localized in the medial forebrain bundle (see Figure 5). Of these four, the tips for one rat bordered on the fornix. Two animals had electrode tips in the H_2 Field of Forel (see Figure 6). One rat had tips localized in the posterior hypothalamic nucleus (see Figure 7) and one animal's electrode tips were placed in the substantia nigra pars reticularis (see Figure 8).

B. Polygraphic Data

Polygraphic data was assessed for a mean of 11.8 hours per day for each rat. Data was assessed for two BL days preceding each platform condition, the fourth and fifth days of each platform condition, and the first, second, and fifth recovery days after each platform condition. Unscorable time comprised 2.9% of total recording time. Unscorable time for each day was proportionately distributed over awake, slow wave sleep, and REM sleep time. Mean time spent in each sleep state is represented by Figures 9 and 10 for L-rats and by Figures 11 and 12 for D-rats.

1. REM Sleep. REM sleep levels are expressed as a percentage of total sleep time. REM percent of total sleep time was significantly correlated with absolute REM time during most conditions (Pearson product moment ranged from $r = .51$, $p < .02$ to $r = .98$ $p < .001$). REM percents did not differ for the two BL conditions for L-rats [$t(7) = .17$, $p > .87$] or D-rats [$t(7) = .72$, $p > .50$]. During each platform condition, REM sleep loss is expressed as the mean REM percent of total sleep time on the fourth and fifth platform day taken as a percent of its respective BL REM percent. Mean percent of REM loss, SWS loss, and total sleep loss for L-rats appear in Table 1. REM sleep loss was significantly greater during RD than LP conditions for L-rats [$T(8) = 4$, $p < .05$, one-tailed], but not for D-rats [$T(7) = 6$, $p > .10$, one-tailed].

Table 2 presents the mean REM percent of total sleep time and the mean total sleep time as a percent of awake time during each sleep condition for L-rats and D-rats. REM percent was significantly elevated over BL levels during recovery days one to two (R12) after RD [$t(7) = 14.78$, $p < .001$] and LP [$t(7) = 4.33$, $p < .003$] for L-rats.

Similarly, R12 REM levels were elevated over BL levels after RD [$t(7) = 15.06$, $p < .001$] and LP [$t(7) = 6.23$, $p < .001$] conditions for D-rats. On the fifth recovery day (R5) REM percents were not higher than BL levels after RD [$t(7) = 2.07$, $p < .08$], but were higher [$t(7) = 7.72$, $p < .001$] during LP for L-rats. For D-rats, this difference was not significant after RD [$t(7) = 1.69$, $p < .14$], but was significant after LP [$t(7) = 2.99$, $p < .02$].

2. Total Sleep Time. Total sleep time is expressed as a percentage of awake time for BL and recovery conditions. During each platform condition, sleep loss is expressed as the mean sleep percent of the fourth and fifth platform days taken as a percent of its respective BL sleep percent. Sleep percent did not differ for the two BL conditions for L-rats [$t(7) = .16$, $p > .8$] or D-rats [$t(7) = .24$, $p > .7$]. Sleep loss did not differ between RD and LP conditions for L-rats [$T(8) = 17$, $p > .10$] or for D-rats [$T(8) = 15.5$, $p > .10$]. During R12 sleep percent was significantly elevated over BL levels after RD [$t(7) = 2.79$, $p < .02$], but fell short of significance after LP [$t(7) = 1.84$, $p > .10$] conditions for L-rats. Sleep levels were elevated over BL levels during R12 after RD [$t(7) = 3.77$, $p < .007$] and LP [$t(7) = 2.89$, $p < .02$] conditions for D-rats. Sleep percent during R5 did not differ from BL levels after RD [$t(7) = 1.90$, $p > .10$] or LP [$t(7) = 0.01$, $p > .99$] for L-rats. Similarly, sleep percent did not significantly differ from BL during R5 and RD [$t(7) = 0.44$, $p > .67$] or LP [$t(7) = 1.22$, $p > .26$] for D-rats.

C. Body Weight

Weight loss during each platform treatment was assessed as the difference in weight between the fifth BL day and the fifth platform

day. As can be seen in Table 3, rats lost weight in response to the platform treatment. There were no significant differences in weight loss due to RD vs. LP conditions for L-rats [$T(8) = 8$, $p > .10$] or D-rats [$T(8) = 12.5$, $p > .10$]. BL weights prior to each of the platform treatments did not differ for L-rats [$T(7) = 6$, $p > .10$] or D-rats [$T(8) = 11$, $p > .10$].

Planned Comparisons

Mean thresholds increased during both RD and LP conditions over BL levels for animals tested in the light and for animals tested in the dark. These differences were significant for both L-rats and D-rats in the BL vs. RD condition [$T(8) = 0$, $p < .005$]. The difference between BL and LP fell short of significance for L-rats [$T(8) = 3.5$, $p < .10$], but was significant for D-rats [$T(7) = 0$, $p < .01$] (see Table 4).

To assess the differential response to RD and LP conditions, two difference scores (RD delta and LP delta) were calculated for each subject by subtracting from the mean RD and LP thresholds the mean of their respective BL thresholds. RD delta was significantly greater than LP delta for L-rats [$T(7) = 0$, $p < .01$]. RD delta did not differ from LP delta for D-rats [$T(7) = 13.5$, $p > .10$] (see Table 5).

All rats tested through the use of the multiple ascending threshold procedure and one L-rat tested in the R50 procedure were treated with amphetamine. Due to a small sample size, thresholds were analyzed as a group. The mean SBE threshold during pre-drug saline conditions was 22 mv. During amphetamine treatment, the mean threshold was 29 mv. A correlated t-test showed a significant elevation in SBE thresholds in response to amphetamine [$t(8) = 2.54$, $p < .04$]. All L-rats and three

of the four D-rats displayed significant elevations in threshold. One D-rat showed a lowering of threshold in response to amphetamine.

Secondary Findings

A. Additional Light-Dark Differences in SBE Thresholds

Table 6 presents the mean SBE thresholds for L-rats and D-rats during each BL, platform, and Recovery condition for L-rats and D-rats. SBE thresholds were elevated over BL levels during R12 subsequent to RD [$T(8) = 0$, $p < .01$], but this difference failed to reach significance during R12 subsequent to LP [$T(7) = 2$, $p < .10$] for L-rats. Similarly, D-rats displayed elevated thresholds during R12 subsequent to RD [$T(8) = 2.5$, $p < .05$] but not subsequent to LP [$T(7) = 3.5$, $p > .10$]. Thresholds on R5 did not differ from BL levels after RD [$T(5) = 4$, $p > .10$] or LP [$T(6) = 8$, $p > .10$] for L-rats or for D-rats [$T(6) = 10$, $p > .10$; $T(5) = 5$, $p > .10$, respectively].

B. Differences Between Threshold Procedure Groups

Table 7 presents mean threshold changes, REM loss, sleep loss, and weight loss during RD vs. LP conditions for rats tested in R50 and multiple ascending procedures. SBE thresholds were differentially altered for the two threshold assessment procedures used. RD delta was significantly greater than LP delta for rats tested through use of the R50 procedure [$T(6) = 0$, $p < .05$]. There was no significant difference between RD delta and LP delta for rats tested using the multiple ascending procedure [$T(8) = 14$, $p > .10$].

REM loss was greater during RD than LP conditions for rats tested in both R50 [$T(8) = 1$, $p < .01$ one tailed] and multiple ascending [$T(7) = 1$, $p < .025$ one-tailed] procedures. Sleep loss did not differ significantly between RD and LP conditions for either R50

[$\underline{T}(8) = 15$, $p > .10$] or multiple ascending [$\underline{T}(8) = 10$, $p > .10$] groups.

Weight loss fell short of reaching a significant difference between the two platform conditions for R50 [$\underline{T}(8) = 6.5$, $p < .10$], and was not significant for the two platform conditions for multiple ascending procedure [$\underline{T}(8) = 8$, $p > .10$].

Post Hoc Findings

A great deal of variability was found in REM sleep levels in response to platform treatment. The mean REM loss and standard deviation scores for each platform condition appear in Table 8. Furthermore, only 12 of the 16 subjects displayed more REM sleep during LP treatment than during RD treatment as compared to respective BL levels. Of these 12, seven rats had REM percent reduced to less than 20% of the BL level during the LP condition. Among the 12 animals for whom REM loss was greater during RD than LP, five were D-rats. The seven L-rats had significantly higher RD delta scores than LP delta scores [$\underline{T}(7) = 0$, $p < .02$]. There were no significant differences in sleep loss [$\underline{T}(7) = 10$, $p > .10$] or weight loss [$\underline{T}(7) = 8$, $p > .10$] for these rats. There were no significant differences in RD delta vs. LP delta for D-rats [$\underline{T}(5) = 6$, $p > .10$].

Using a Mann-Whitney U-test, it was found that rats tested in the R50 procedure exhibited significantly less REM loss than those tested in the multiple ascending procedure for both RD [$\underline{U}(8,8) = 13$, $p < .05$] and LP [$\underline{U}(8,8) = 6$, $p < .01$] conditions. There were no differences in sleep loss [$\underline{U}(8,8) = 16$, $p > .10$; $\underline{U}(8,8)$ 14.5, $p > .10$] or weight loss [$\underline{U}(8,8) = 20$, $p > .10$; $\underline{U}(8,8) = 29$, $p > .10$] for RD or LP conditions between animals tested in R50 or multiple ascending procedures, respectively.

DISCUSSION

Interpretation of Results

The data resulting from this experiment suggest that feeding may be inhibited in response to REM sleep deprivation. Those animals tested in the light displayed significantly greater SBE threshold elevations over BL levels in response to small platform treatment than LP control treatment. That the difference in threshold change can be attributed to REM deprivation is supported by the fact that rats were significantly more REM deprived during the small platform condition than during the LP condition. Since there were no significant differences in the percent of sleep loss between LP and RD conditions, this effect is probably not the result of non-specific sleep loss. In addition, since weight loss in response to the two platform treatments did not differ, it is unlikely that SBE threshold elevations can be attributed to body weight changes. Furthermore, thresholds remained elevated over BL levels on the first two recovery days subsequent to RD, and returned to BL levels by R5. During R12 subsequent to LP treatment, SBE thresholds were no longer significantly elevated over BL threshold levels.

For rats tested in the dark, the data are less conclusive. Although the percent of sleep loss and the weight loss did not differ between the RD and LP conditions, three of the eight rats were not more REM deprived during the RD than the LP condition. Therefore, the two platform manipulations were not effective in achieving differential REM deprivation. However, even if these subjects are eliminated, there is no difference in threshold elevation between RD and LP conditions.

There exist several possible explanations for the lack of differ-

ential changes in SBE thresholds for RD and LP conditions in the D-rats. Since treatment manipulations were effective in only five of the dark subjects, it is possible that the effect was masked by too few subjects. This explanation seems unlikely, however, since two subjects had large effects in the opposite direction. That is, for two subjects threshold elevations were greater during LP than RD.

Alternatively, it is possible that the effect of REM deprivation on the neural substrate mediating SBE is the same during the light and dark, but that testing during the dark presents a measurement problem. Under standard feeding conditions, animals eat twice as much in the dark as in the light (see above). When measuring SBE thresholds after a satiation period, it is assumed that the animal's operant level for feeding is close to zero. To the extent that this assumption is true, the threshold obtained reflects the sensitivity of the functional system that is activated by the stimulation. However, since normal feeding is probably determined by many systems, to the extent that these other systems are activated, the selective influence on feeding of the system in question is clouded. If, in fact, animals had a higher operant level for feeding during testing in the dark, then the influence of REM deprivation on feeding mediated by the neural substrate of SBE behavior may be less apparent at that time. This may account for the fact that REM deprivation did not differentially effect SBE thresholds for the five D-rats for whom the platform treatments were effective in differentially altering REM sleep. It is possible that SBE thresholds are not raised by REM deprivation in the dark. Alternative explanations, however, have not been ruled out.

The hypothesis that REM deprivation would result in opposite effects

on SBE thresholds under light vs. dark testing conditions has not been confirmed. In all platform conditions, D-rats were REM deprived to some degree, and SBE thresholds were elevated. Although the failure to achieve differential REM deprivation, and the possible interfering effects of high operant feeding levels leave unresolved the question of whether REM deprivation affects SBE thresholds assessed in the dark, it seems highly unlikely that these problems are masking a facilitation of SBE.

That amphetamine elevated SBE thresholds for eight of the nine rats tested, and that electrode tips for most rats were localized in and around the medial forebrain bundle, support the assumption that the feeding behavior elicited in this experiment has the motivated qualities described by Coons and co-workers (1965).

The variability in REM deprivation and the degree of sleep loss in response to platform treatment calls into question the use of the inverted flower-pot technique for future research. This variability is not correlated with body weight. Because of the high propensity for animals to have REM sleep when REM deprived, and therefore the tendency to adapt to stimuli used to awaken them when they exhibit REM sleep, only stressful procedures, or drug treatment, are effective as REM derpivation agents. Stressful procedures unavoidably result in large quantities of sleep loss. However, sleep loss can be measured, and if levels are equated for experimental and control groups, it can be assumed that sleep loss is not solely responsible for any alterations in the dependent variable. Alternatively, drug effects may be more complicated and less easily measured. Therefore, if one wishes to utilize REM deprivation manipulations, it seems that the flower-pot

technique may still be the preferred method. However, because of the variable response to the platform treatment, no assumptions regarding the degree of REM deprivation can be made in the absence of polygraphic sleep data. In addition, it would enhance the validity of this manipulation if an independent measure of stress were employed. Because of the rarity of a REM augmentation response, it seems that REM deprivation is an indisposable manipulation in the investigation of the behavioral function of REM sleep.

The differential level of REM deprivation achieved for animals tested under the R-50 vs. multiple ascending procedures merits further investigation. The R-50 animals tended to receive longer stimulation sessions at similar intensities, and therefore received more stimulation. Spielman and others (1974) report that ICSS results in lower than BL levels of REM sleep, and Steiner and Ellman (1972) report a decreased REM rebound after REM deprivation if rats are administered ICSS. Since SBE brain sites also support ICSS behavior, it would seem likely that R-50 animals would have less REM pressure and therefore less REM sleep than multiple ascending animals during REM deprivation. It is possible that distinct brainsites support ICSS and SBE. Olds and others (1971), using small electrodes, report on SBE sites that do not support ICSS. Alternatively, since stimulation parameters are very different for ICSS (1/4-sec. train, response contingent) and SBE (30 continuous sinusoidal wave -- not response contingent, low current intensity), it is possible that stimulation of the same site results in activation of distinct neural sub-systems that bear oppostie relationships to the neural system mediating REM sleep. It is known that animals will work to turn off stimulation administered in the temporal pattern and current

intensity identical to that which they previously worked to turn on (Steiner, Beer & Shaffer, 1969). Thus, the activation of reward systems may be time-locked to a patterning of neural firing within the animal. Decreased REM pressure may be dependent upon activation of this sort of reward system.

The difference in threshold elevation between RD and LP conditions was significant for rats tested in R50, but not multiple ascending procedures, and light-, but not dark-tested rats. It should be noted that, to a great extent, these findings are influenced by two rats who exhibited larger SBE threshold elevations during LP than RD conditions. Both had less REM sleep on the small platform than on the LP. Both rats were tested in the multiple ascending-dark condition. Electrode placements for both subjects were in the medial forebrain bundle. For one, the tips bordered the fornix. Both rats responded to amphetamine with elevated thresholds. Furthermore, neither had anomalous weight loss or sleep loss in either the RD or LP condition. It cannot be determined, from so small a group of subjects, whether these reversed effects are attributable to the combined effect of the testing procedure and the lighting condition, or whether they represent random variability.

Theoretical Considerations

The results of this study support the hypothesis that REM deprivation inhibits SBE, and that normal feeding behavior may be altered during REM deprivation. In addition, SBE thresholds remain elevated during the REM rebound recovery period. During this time, although the rats exhibit high levels of REM sleep, they can be considered to have a high "REM pressure" or need for REM sleep, i.e., to still be REM deprived.

That REM deprivation inhibits feeding, seems to be contradictory to the findings of Seigel (1975). As reported above, during normal conditions Seigel found a negative correlation between REM percent on a given night, and feeding on the subsequent day. The previously-held interpretation of Seigel's findings, that low REM levels result in increased waking drive behavior, support the drive hypothesis. Alternatively, it is possible that high REM levels on a given night reflect a state of increased "need" for REM sleep, or high REM pressure, and thus, result in feeding inhibition. Conversely, low level REM nights may reflect a state of low REM pressure and may therefore result in more feeding. This explanation is highly speculative, but nonetheless testable. It would be of interest to assess whether either SBE thresholds or thresholds for foot-shock induced fighting correlate with normal REM sleep levels. According to the interpretation of Seigel's data posed here, aggression thresholds should correlate negatively with REM levels on the previous night, and SBE thresholds should correlate positively with the previous night's REM levels during undisturbed conditions. It may be possible to further explore the nature of the suppressed feeding response by measuring alterations in meal patterns and taste sensitivity in response to REM deprivation.

The results of this study do not support the hypothesis that REM deprivation results in effects similar to, or the opposite of those resulting from NE injection. Although the lack of effect in the D-rats is not conclusively attributable to any single factor, since differential REM deprivation between platform conditions was not achieved, all animals did display significantly elevated thresholds above baseline levels. If the results paralleled those of Margules (1972), then

thresholds should have been lowered by REM deprivation during one of the lighting conditions. The failure to confirm this hypothesis must be considered in light of Leibowitz' findings, that the catecholaminergic influence on feeding through intracranial injection is highly dependent on neuroanatomical site of injection. Leibowitz (1978c) has found no circadian variability in response to injections to the paraventricular or perifornical sites she has defined. Cannula placements in the study reported by Margules and co-workers (1972) were localized in the perifornical lateral hypothalamus. Although these findings were replicated (Stern & Zurik, 1973), an opposite trend in cyclicity of NE elicited feeding was reported by Armstrong and Singer (1974) after NE injection to the lateral ventricles. In light of the need for neural specificity, the interpretation of any findings are limited in terms of their implications regarding feeding behavior and REM sleep.

The modulatory influence exerted on REM sleep by NE may be complex. Since the occurrence of REM sleep seems to be linked to the cessation of firing of serotonergic raphe units, a critical ratio of NE to serotonin levels may determine activation of the REM sleep mechanism. REM deprivation may result in an imbalance of this critical ratio.

Dement (1969) and McGinty and co-workers (1974) suggest that serotonin inhibits drive behavior and that REM sleep occurs when serotonin levels are low. Serotonin depletion is known to result in increased hallucinatory, aggressive and sexual behavior (see McGinty et al., 1974). McGinty and others (1973) suggest that sleep-wake states may be determined by the degree of coupling of NE and serotonin systems. He suggests that the monoamines may control the coupling of functional systems

that mediate sensory input, cognition, pre-motor and motor output. REM sleep, they speculate, may reflect an uncoupling of these systems. This uncoupling results in pre-motor unit firing in the absence of motor output, and the lack of integration of cognition and sensory input known to occur during REM sleep.

If, in fact, REM derpivation elevates SBE thresholds only when tested in the light, then it would be meaningful to understand that phenomenon in the context of the way other related behaviors occur with respect to the light-dark cycle. It is known that most behaviors occur more frequently in the dark in rats. Feeding, sexual behavior and activity levels are all higher in the dark (Lockard, 1963). Rats maintained on a L-12, D-12 lighting schedule sleep more in the light than in the dark (Fishman & Roffwarg, 1972); however, it has been shown that this is not because light enhances sleep behavior. In fact, given a choice situation, rats spend 95% of their time in the dark, and sleep exclusively in the dark (see Fishman & Roffwarg, 1972). Furthermore, Fishman and Roffwarg present data suggesting that exposure to light selectively REM deprives rats. Whitehead, Fredrickson, Wincor, Madensky and Rechtschaffen (1970) and Lisk and Sawyer (1966) have shown that dark conditions elicit REM sleep. It may be the case that non-specific drive energy (perhaps manifested by REM sleep or ICSS) is enhanced in the dark. If, under normal conditions, feeding is the result of hunger and nonspecific drive energy, then REM deprivation may be enhancing the non-specific drive component and suppressing the hunger component of the response. These effects could cancel each other and result in no change in feeding behavior measured in the dark in response to REM deprivation.

The various theoretical positions as to the behavioral function of

REM sleep are, to some extent, compatible. For example, the sentinel hypothesis explains the evolutionary advantage that REM sleep afforded ancient mammals. This theory offers few comments on the present link between REM sleep and waking behavior, but is compatible with either the drive, or drive-reward theory. Snyder (1966) notes that during circumstances of environmental stress (when an animal would be REM deprived), it might be advantageous for an organism to have a high drive level.

Since REM deprivation does occur naturally in response to particular environmental conditions, it seems important that a behavioral theory of REM sleep explain its mediating role between environment and behavior. The drive theory explains REM sleep as regulating behavior in response to varying endogenous states of the organism, but fails to explain REM variability in response to environmental conditions. Furthermore, it is difficult to conceive of why it would be adaptive for all drive behaviors to be energized at the same time. In particular, under what circumstances would it be advantageous to energize feeding and aggression at the same time?

Extending Snyder's reasoning to more recent notions stated in the drive-reward hypothesis, it would be advantageous for REM deprivation to result in an enhanced sensitivity to predatory threats, facilitation of aggressive (fight or flight) behaviors, and an inhibition of behaviors associated with feeding.

The information-consolidation theory is less compatible with the sentinel hypothesis. It seems unlikely that, if REM sleep aids in consolidation, an organism would be well served to be REM-deprived during stressful circumstances.

Taken alone, the main limitation of the sentinel hypothesis regards the paucity of testable predictions it posits. In fact, according to this notion, REM sleep may represent a vestigial process for some organisms. Snyder speculates that the function of REM sleep may have evolved along with the changing needs of the organism in suggesting that early morning awakenings frequently observed in depressive patients may be a response to an endogenous danger signal.

The drive hypothesis specifies the particular behaviors that are regulated by the REM sleep mechanism, as well as the nature of their inter-relationship. This would seem to lead to testable hypotheses. A major problem, however, lies in the fact that, since the behaviors in question are crucial to survival of the organism, they tend to be behaviors that are over-determined. That is, these behaviors are organized on many levels of the nervous system, and therefore may tend not to be disrupted by a single manipulation such as REM deprivation. The unique advantage of the drive-reward hypothesis lies in its specification of a neural substrate of behavior that can be taped and sensitively measured. If the system in question is linked to REM sleep, then its response to REM deprivation should be observable even if another system offers behavioral compensation. Furthermore, the system specified by the drive-reward hypothesis is known to be associated with rewarding and motivational aspects of behavior. Thus, in the case of feeding, the behavior can be measured in terms of a particular system, and the measure is relatively unaffected by compensatory mechanisms that may maintain body weight and nutritional needs in the face of challenges imposed by REM deprivation.

The information-consolidation hypothesis proposed by Fishbein

(1970, 1971) is internally inconsistent. Fishbein suggests that the consolidation mechanism is differentially affected by REM deprivation depending upon whether training of a passive avoidance task occurred before or after the REM deprivation procedure (see above). Fishbein's hypothesis does not differentiate among tasks to be affected by REM deprivation. Rather, his notion suggests that the critical role of REM sleep is linked to a particular processing stage, and therefore, his predictions differentiate along a time course after training. Pearlman and Greenberg's data, that simple tasks are disrupted by REM deprivation, provide contradictory evidence to Fishbein's hypothesis. Since Fishbein utilized a passive avoidance task (while Pearlman and Greenberg use active tasks) and since he failed to employ procedures to control for the increased activity levels found to occur in response to REM deprivation, limitations are placed on the interpretation of his findings.

Pearlman and Greenberg's notion that REM-dependent behaviors comprise those tasks that involve complex stimulus conditions offers an explanation for the appearance of REM sleep in mammalian evolution. They reason that mammals need to depend on newly acquired information and consolidation of stimulus contingencies for survival more than pre-mammalian organisms. Thus, they view the evolutionary development of REM sleep as an adaptation that facilitates consolidation of information necessary for behaviors that are important for survival, but that are not "pre-wired" into the brain.

The major strength of this hypothesis lies in its ability to predict disruption of some behaviors, but not others. These behaviors are easily specifiable, and can be easily measured. Pearlman and Greenberg

interpret their findings as lending support to their theory. Their studies support the notion that REM deprivation disrupts performance of tasks involving complex stimulus conditions, and not simple conditions. None of their manipulations, however, address the issue of whether the disruption is attributable to pre-consolidation mechanisms (such as selective attention), or consolidation mechanisms. During amphetamine treatment, performance of complex tasks tends to be disrupted. These effects are generally attributed to either alterations in selective attention, or response compatibility rather than consolidation mechanisms. If, as suggested here, REM deprivation prepares the organism for predatory challenge, then sensitivity to particular stimuli may be enhanced at the expense of other, more complex stimuli. Furthermore, Pearlman and Greenberg utilized food as a reinforcer in their experiment. If stimuli relating to feeding behavior are less potent during REM deprivation, then learning of a complex task in order to obtain food would be inhibited. The drive-reward theory provides a model for investigating the relationship of REM sleep to reward-related behaviors. This model is based on evidence that the ICSS neural network is reciprocally related to brain mechanisms mediating REM sleep, and the assumption that stimulus-bound behaviors elicited from brain sites that support ICSS behavior reflect the motivation component of the behavior. This model provides a means of precisely measuring the sensitivity of the neural substrate of various consumatory and appetative behaviors from brain sites known to be related to reward mechanisms. It thereby potentiates investigation of the organization of reward systems and their relationship to REM sleep. Since many stimulus-bound behaviors can be elicited from more posterior brain sites without the

motivational response quality seen in hypothalamically elicited responding, the importance of the motivational (as opposed to sensory input or motor) component of the response can be assessed.

In accordance with the drive-reward model, it is suggested here that REM sleep may serve the fuction of modulating the degree of activation of an organism to respond to a predatory challenge. Since animals respond to environmental stress by having less REM sleep, REM sleep may serve as a mediator between environmental conditions and endogenous levels of activation. This endogenous activation may result in enhancement of some behaviors and suppression of others. Specifically, it is proposed that REM deprivation results in activation of response patterns associated with sympathetic nervous activation. This notion gains support from the fact that the behavioral effects of REM deprivation are analogous to those of amphetamine.

This hypothesis suggests that the behavioral effects of REM deprivation are mediated by the same mechanisms as those mediating the behavioral effects of amphetamine. Like amphetamine, REM deprivation is hypothesized to exert peripheral effects reflecting sympathetic nervous system activation. These physiological changes predispose the organisms to emit adaptive behaviors in the face of predatory challenge. Thus, the drive-reward hypothesis is compatible with Snyder's explanation of the phylogenetic basis of REM sleep. That REM deprivation suppresses SBE from brain sites where it is known to enhance ICSS, strengthens the hypothesis that amphetamine and REM deprivation exert their influence on behavior through the same mechanisms.

The finding that REM deprivation interferes with performance of

complex, but not simple tasks are also analogous to the behavioral effects of amphetamine. It is not necessarily the case, however, that these effects are due to disruption of a memory-consolidation mechanism. Alternatively, it may redirect attention to environmental danger signals.

Table 1: Means and Standard Deviations for REM (percent of total sleep time), SWS (percent of total sleep time) and Total Sleep (TS) (percent of awake) All as Percents of BL Levels.

		R D			L P		
		REM	SWS	TS	REM	SWS	TS
L-rats	$\bar{X}$	7.2	116.4	34.5	24.0	113.0	35.5
	sd	8.0	4.4	6.4	30.7	5.4	13.4
D-rats	$\bar{X}$	14.7	114.3	44.6	31.4	111.9	43.5
	sd	24.4	6.3	17.7	29.5	6.9	20.5

Table 2: Means and Standard Deviations of REM as a Percent of Total Sleep Time, and Total Sleep Time as a Percent of Awake Time for L-rats and D-rats During each Sleep Condition

			BL	RD	R12	R5	BL	LP	R12	R5
L-rats	REM%	$\bar{X}$	15.0	1.0	28.5	16.8	14.8	3.7	24.8	17.5
		sd	1.8	1.2	3.1	1.3	2.4	4.8	5.7	2.2
	sleep%	$\bar{X}$	145.0	48.1	233.1	165.3	143.2	51.6	174.1	143.1
		sd	48.5	10.1	79.8	35.3	45.0	27.9	54.0	37.9
D-rats	REM%	$\bar{X}$	14.0	1.7	27.1	16.2	14.5	4.4	25.8	16.5
		sd	2.6	2.5	2.9	2.7	2.1	4.1	4.5	2.3
	sleep%	$\bar{X}$	150.2	65.7	228.9	156.4	148.0	64.3	226.2	168.9
		sd	30.3	28.1	60.9	39.5	31.7	32.5	79.4	31.6

Table 3: Means and Standard Deviations of Body Weight for L-rats and D-rats Pre- and Post-RD and LP Conditions (gms).

		Pre-RD	RD	Pre-LP	LP
L-rats	$\bar{X}$	510	481	523	494
	sd	28	24	33	36
D-rats	$\bar{X}$	532	481	523	484
	sd	61	24	60	54

Table 4: SBE Threshold Means and Standard Deviations for RD and LP Conditions and Their Respective BL Conditions, for L-rats and D-rats (mv).

		BL	RD	p	BL	LP	p
L-rats	$\bar{X}$	20.3	28.8	*	21.6	25.1	ns
	sd	9.8	9.8		7.6	8.4	
D-rats	$\bar{X}$	15.9	24.1	*	15.7	26.0	*
	sd	4.2	10.1		5.2	16.4	

* $p < .05$

ns $p > .05$

Table 5: Mean and Standard Deviation of Increase Over BL in SBE Thresholds During RD and LP for L-rats and D-rats (mv).

		RD delta	LP delta	p
L-rats	$\bar{X}$	8.6	3.6	*
	sd	4.8	4.6	
D-rats	$\bar{X}$	8.3	10.3	ns
	sd	7.2	13.1	

* $p < .05$

ns $p > .05$

Table 6: SBE Threshold Means and Standard Deviations During Each Sleep Condition for L-rats and D-rats.

		BL	RD	R12	R5	BL	LP	R12	R5
L-rats	$\overline{X}$	20.3	28.8	23.0	19.2	21.6	25.1	23.3	21.4
	sd	9.8	9.8	9.4	7.3	7.6	8.4	7.8	7.7
D-rats	$\overline{X}$	15.9	24.1	19.6	16.3	15.7	26.0	19.0	15.4
	sd	4.2	10.1	6.7	5.8	5.2	16.4	7.8	6.0

Table 7: Means and Standard Deviations of Threshold Change, REM Loss, and Weight Loss During RD and LP Conditions for Rats Tested in R-50 and Multiple Ascending Procedures.

	R-50			Multiple Ascending		
	$\bar{X}$	sd	p	$\bar{X}$	sd	p
Thresholds (mv)						
RD delta	6.0	3.0	*	10.8	5.8	ns
LP delta	2.2	1.5		4.3	7.0	
REM Loss (%)						
RD	18.1	23.9	*	3.8	2.3	*
LP	46.6	31.5		8.9	6.3	
Sleep loss (%)						
RD	45.6	14.2	ns	33.5	11.3	ns
LP	48.1	19.8		30.9	8.7	
Weight Loss (g)						
RD	42	9	ns	18	29	ns
LP	34	15		27	24	

* $p < .05$

ns $p > .05$

Table 8: Means and Standard Deviations of REM Loss (expressed as REM percent of total sleep time as a percent of BL) During RD and LP Conditions for L-rats and D-rats.

		RD	LP
L-rats	$\bar{X}$	7.2	24.0
	sd	8.0	30.7
D-rats	$\bar{X}$	14.7	31.4
	sd	24.4	29.5

FIGURE LEGENDS

Figure 1: Schematic of Experimental Design.

Figure 2: Schematic of electrode placements of the six L-rats with electrode tips in the medial forebrain bundle.

Figure 3: Schematic of localization of electrode in the fornical area for one L-rat.

Figure 4: Schematic of electrode placement for one L-rat with electrode tip in the H2 field of Forel.

Figure 5: Schematic of electrode placements of the four D-rats with electrode tips in the medial forebrain bundle.

Figure 6: Schematic of electrode placements of the two D-rats with electrode tips in the H2 field of Forel.

Figure 7: Schematic of electrode placement for one D-rat with electrode tip in the posterior hypothalamic nucleus.

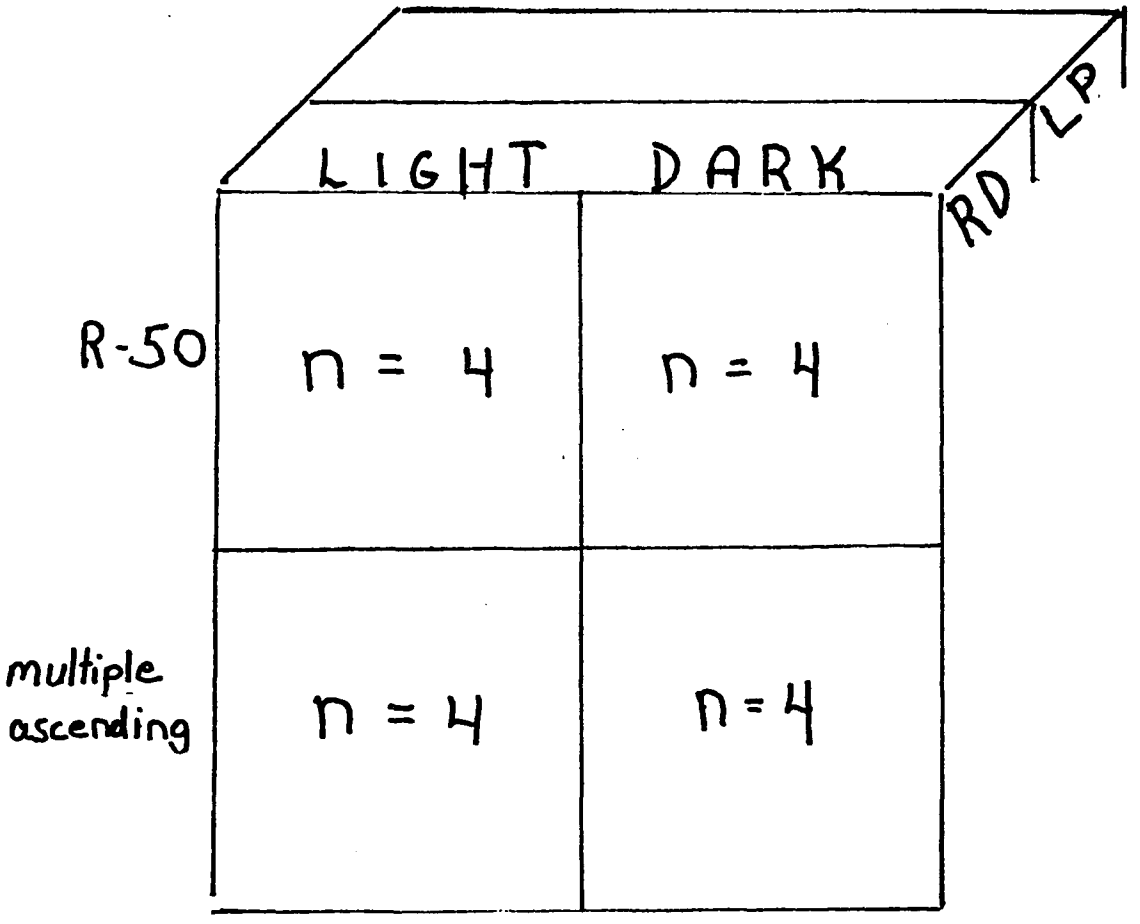
Figure 8: Schematic of electrode placement for one D-rat with electrode tip in the substantia nigra pars reticularis for one D-rat.

Figure 9: REM time, SWS time and Awake time during BL, RD and Recovery conditions for L-rats.

Figure 10: REM time, SWS time and Awake time during BL, LP and Recovery conditions for L-rats.

Figure 11: REM time, SWS time and Awake time during BL, RD and Recovery conditions for D-rats.

Figure 12: REM time, SWS time and Awake time for BL, LP and Recovery conditions for D-rats.



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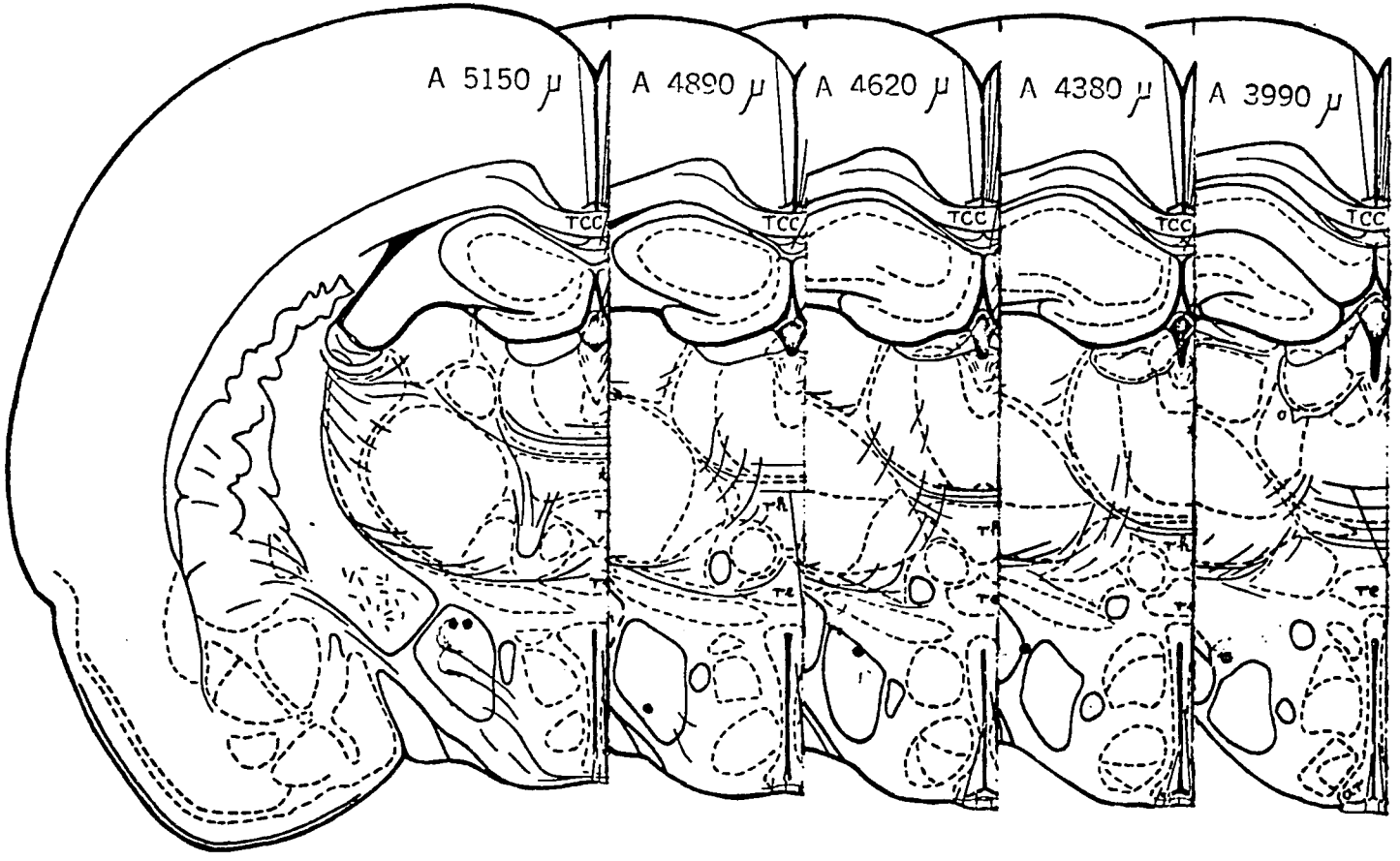

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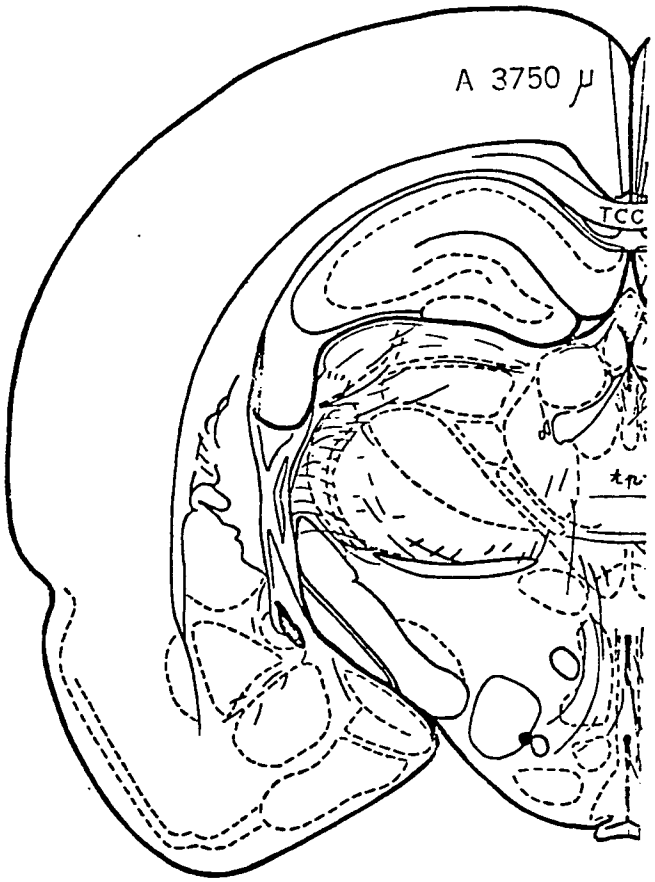

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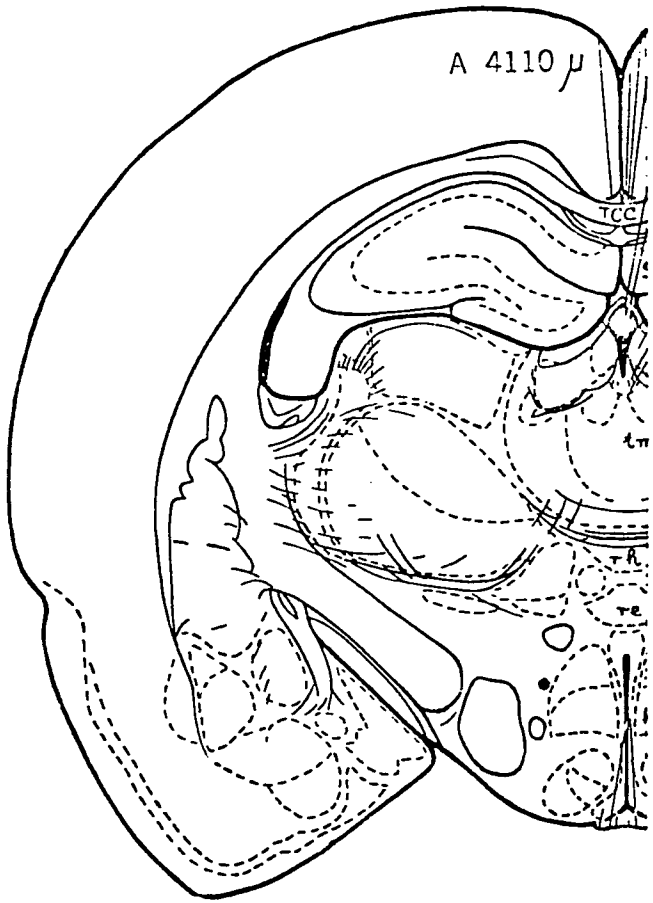

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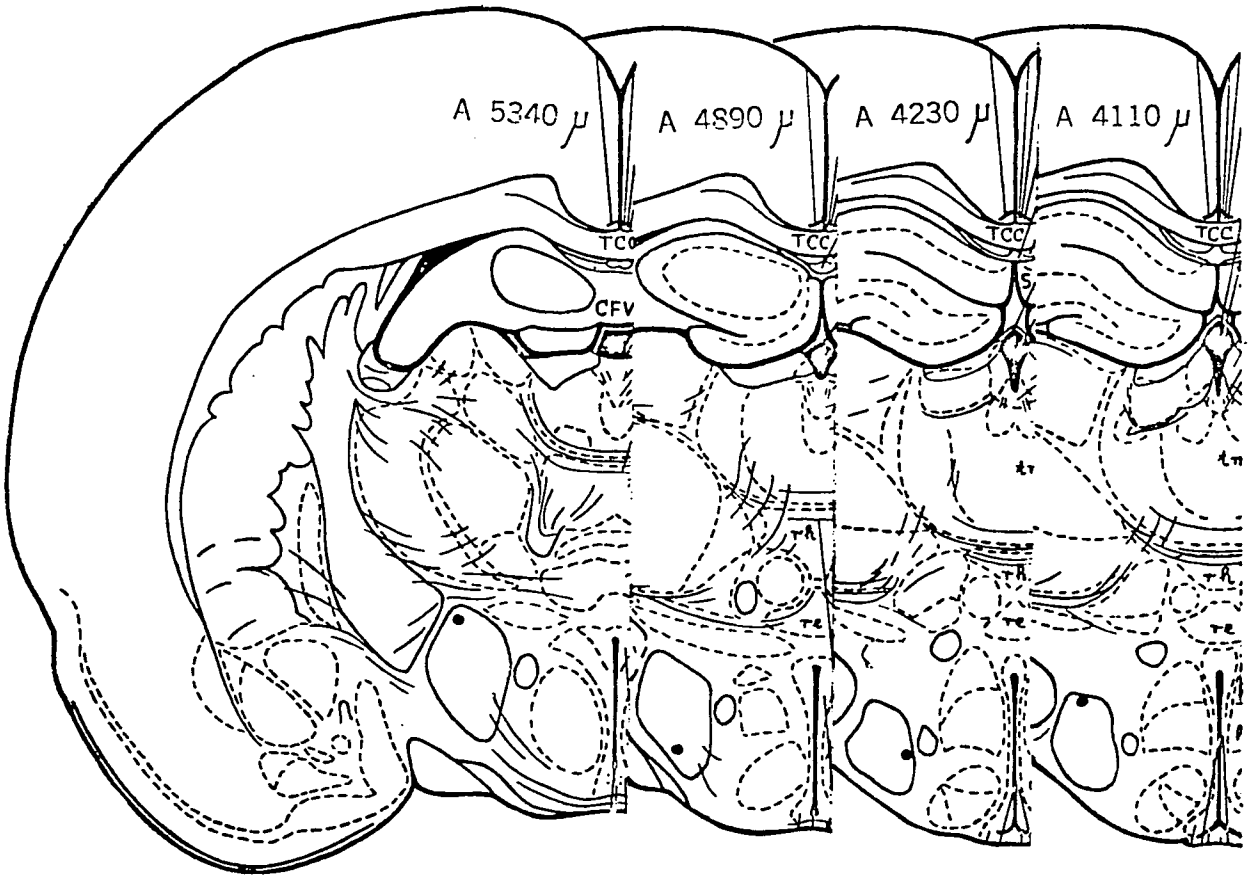

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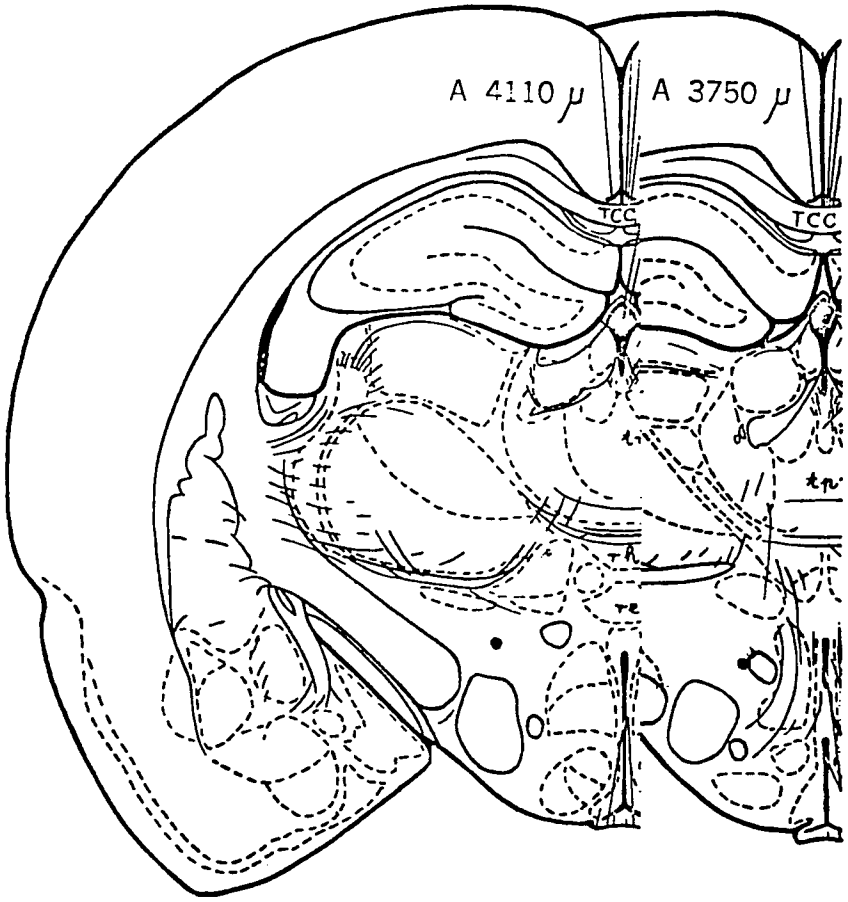

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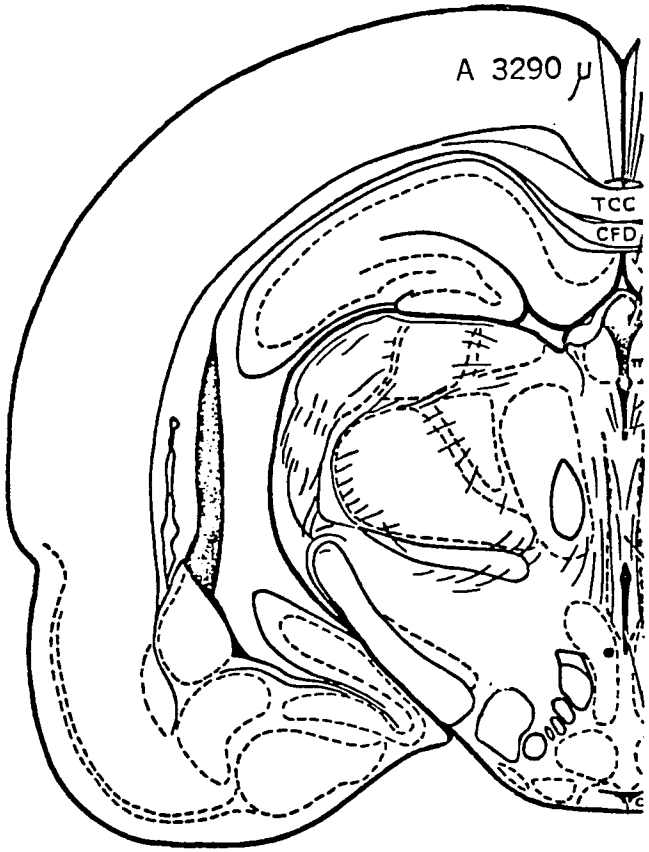

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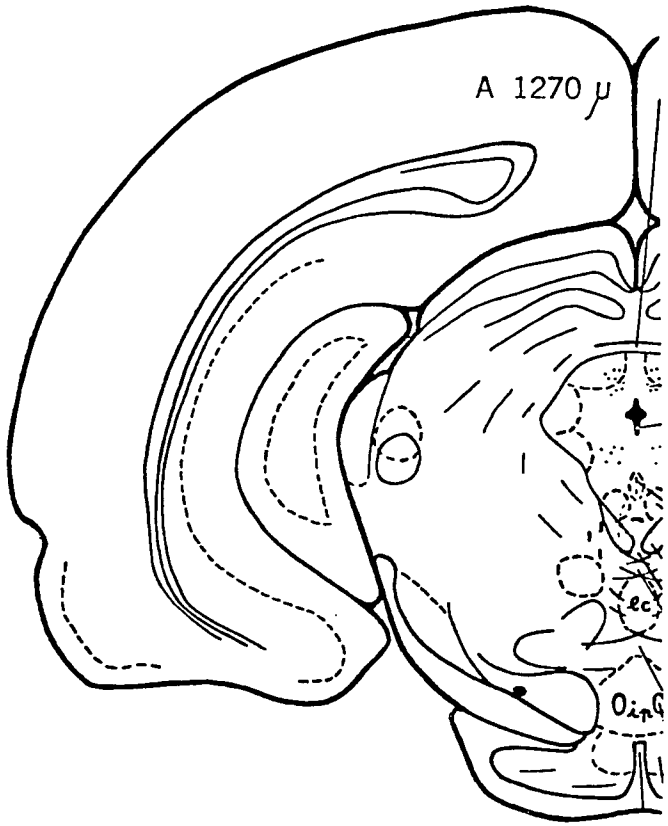

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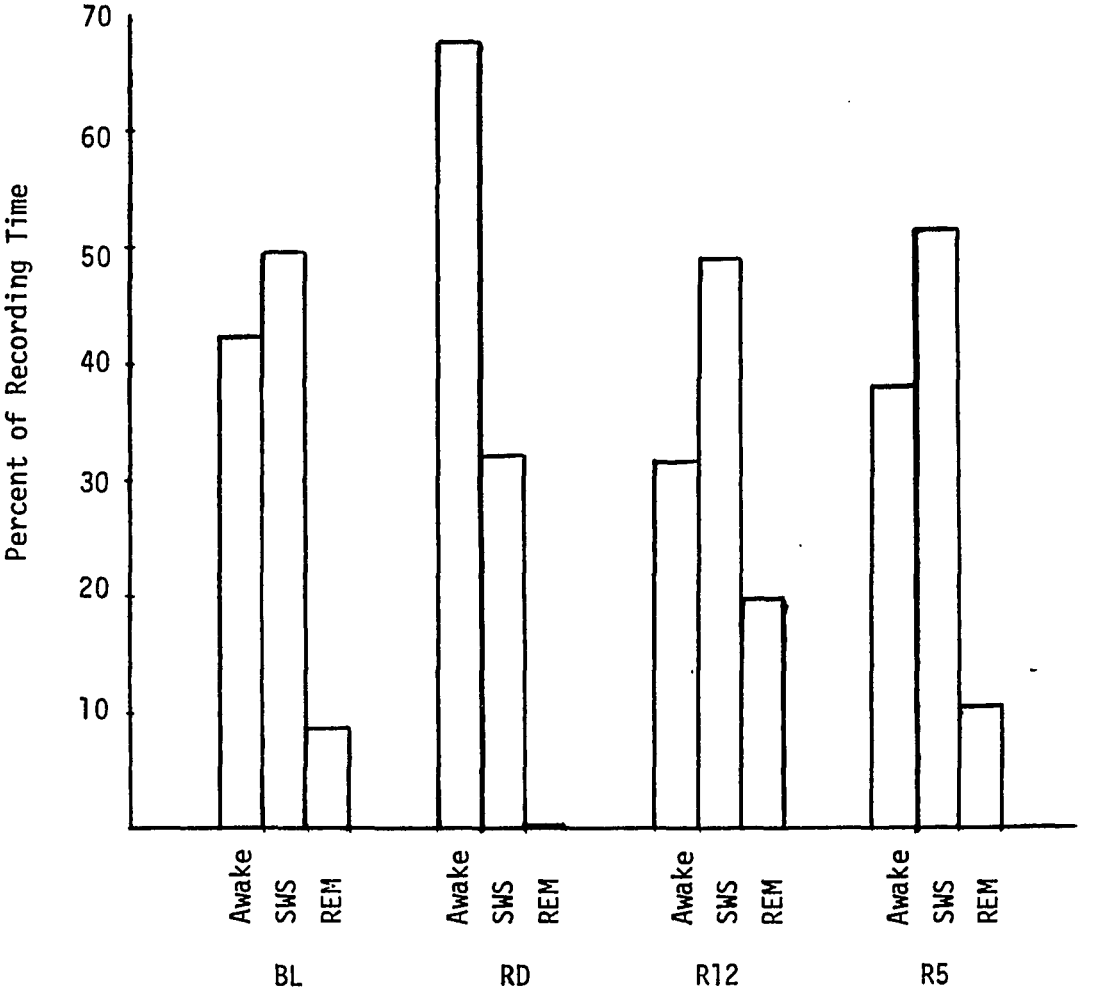
Percent of Recording Time
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Awake
SWS
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R12
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Figure 9

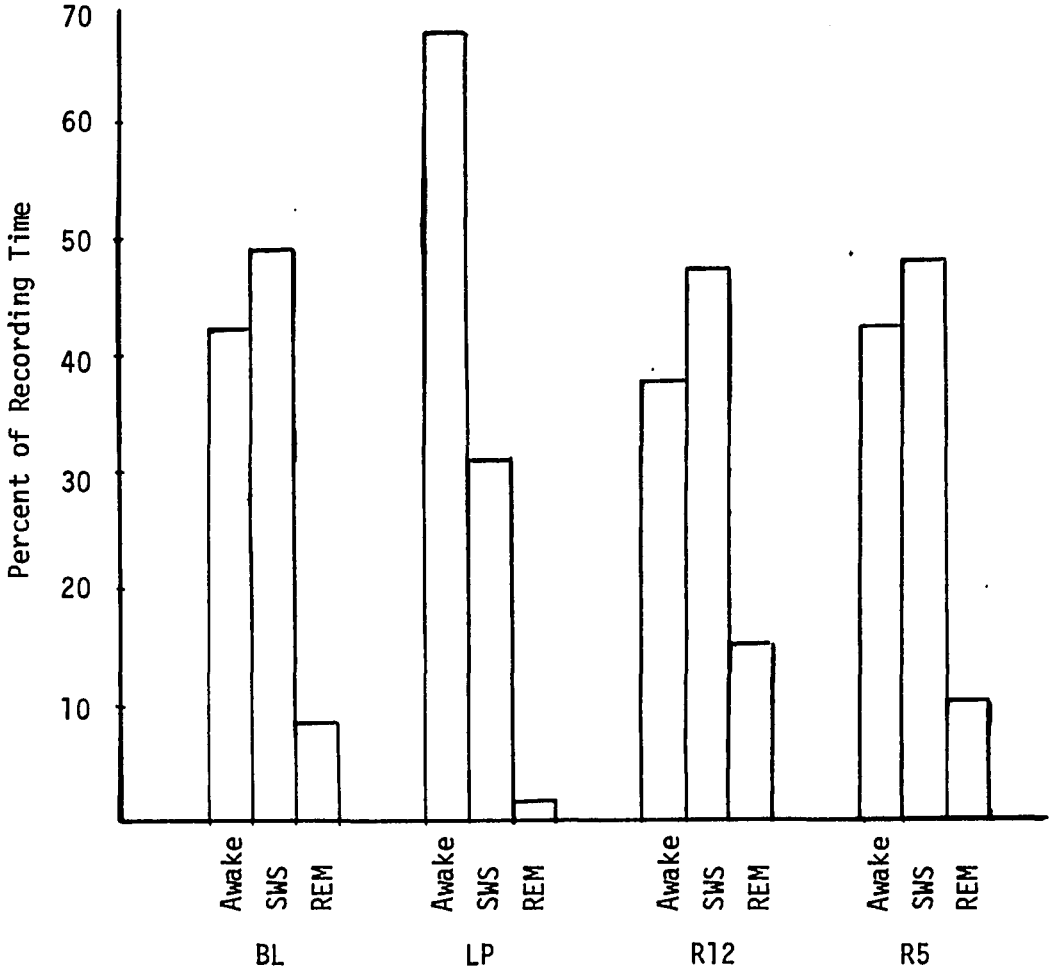
Percent of Recording Time
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Figure 10

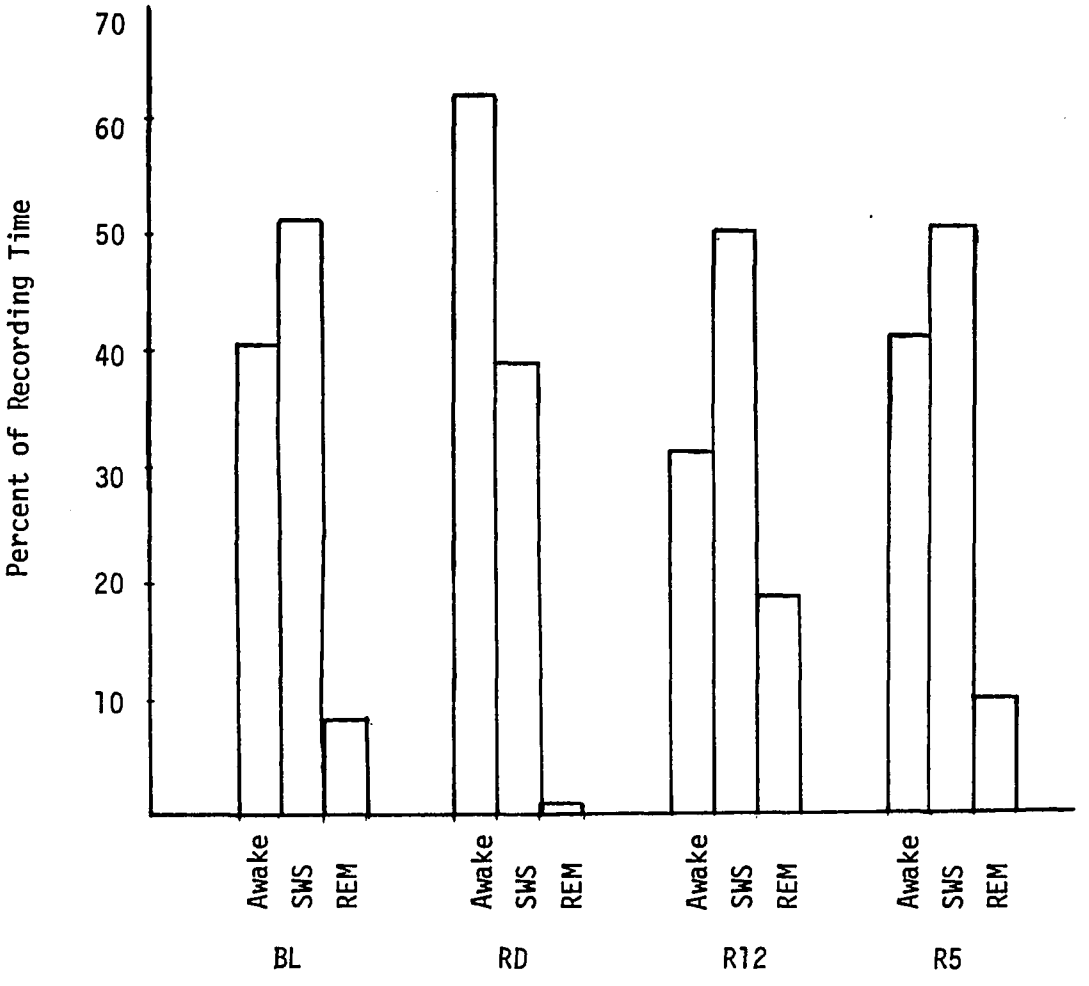
Percent of Recording Time
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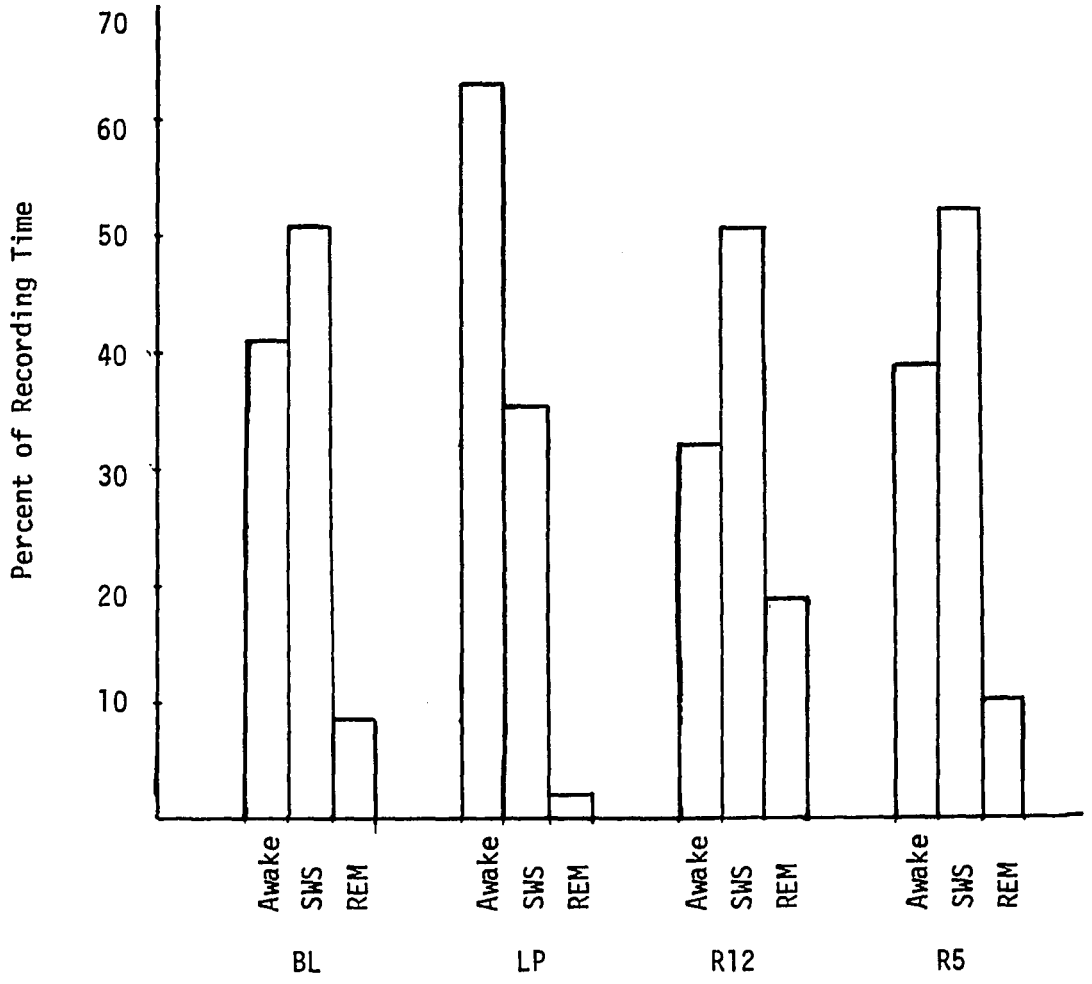
Figure 11


Percent of Recording Time
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Awake
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REM
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R12
R5

Figure 12

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